HOW SIDE REACTIONS CAN INFLUENCE POLY(2-OXAZOLINE) SYNTHESIS FOR POLYMER THERAPEUTICS AND HYDROGELS

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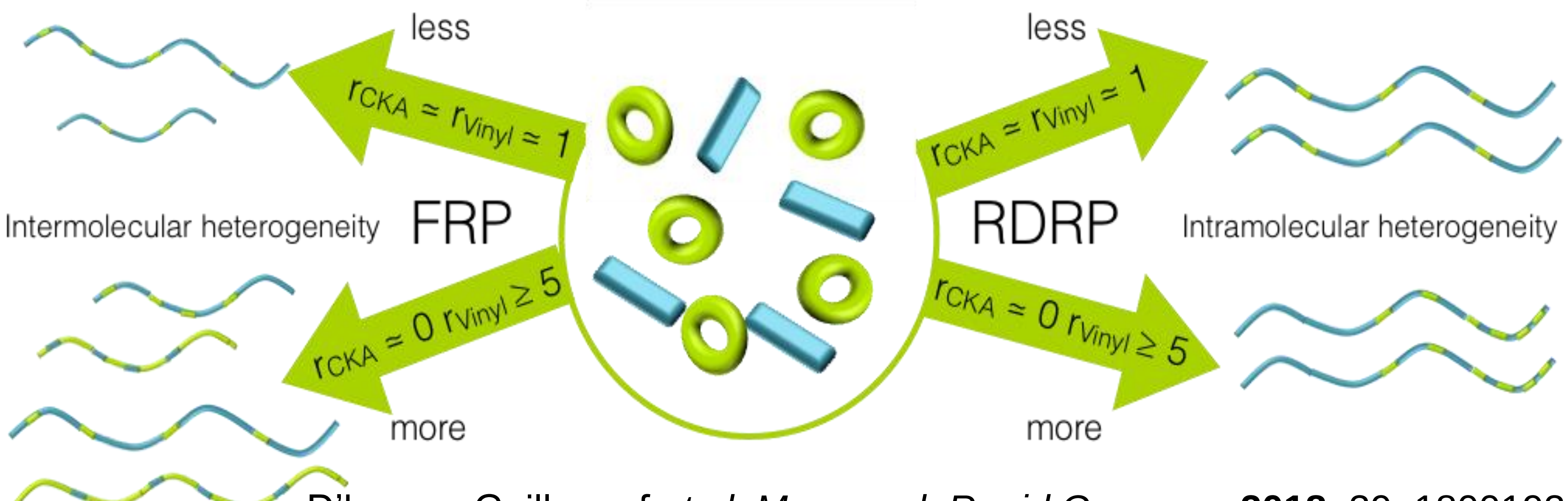
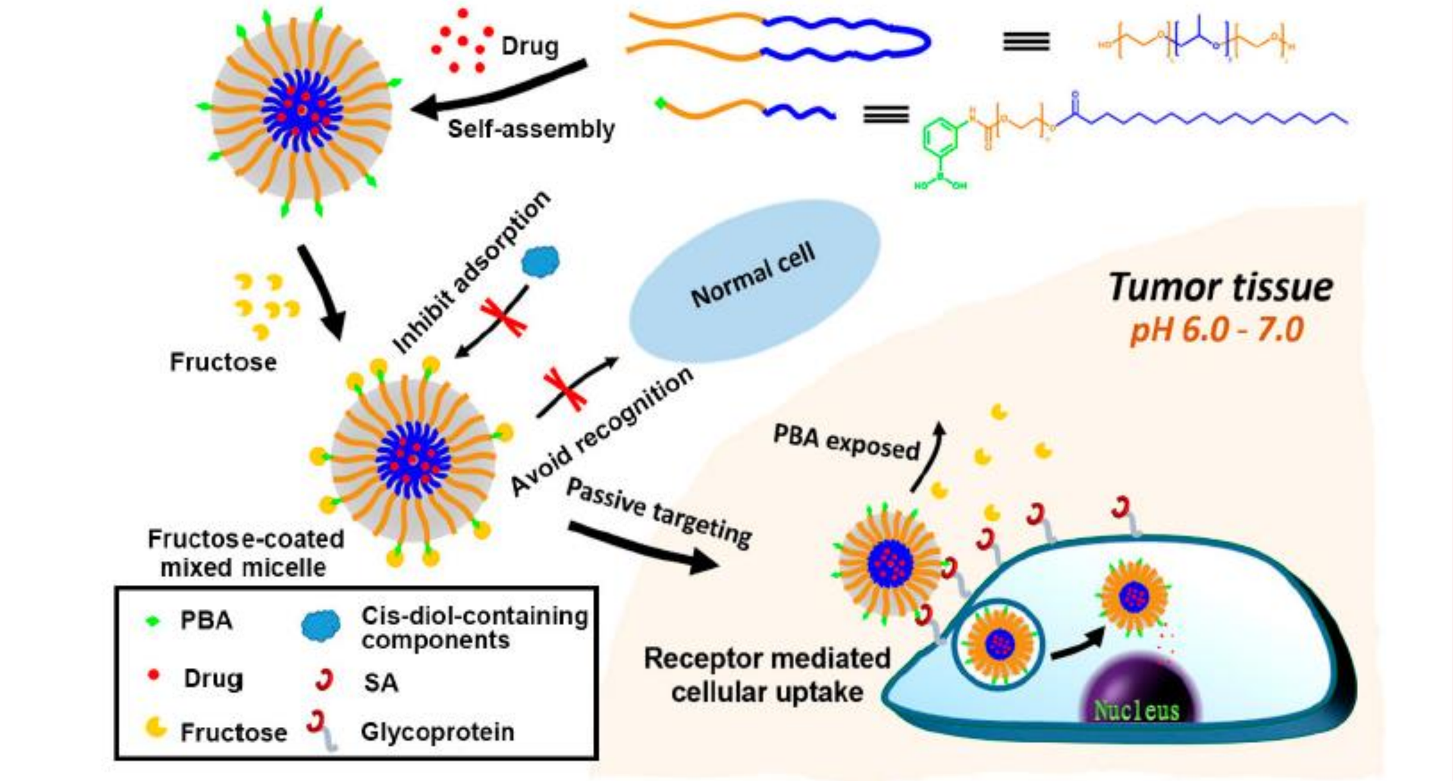
[3]Centre for Textile Science and Engineering (CTSE), Ghent University

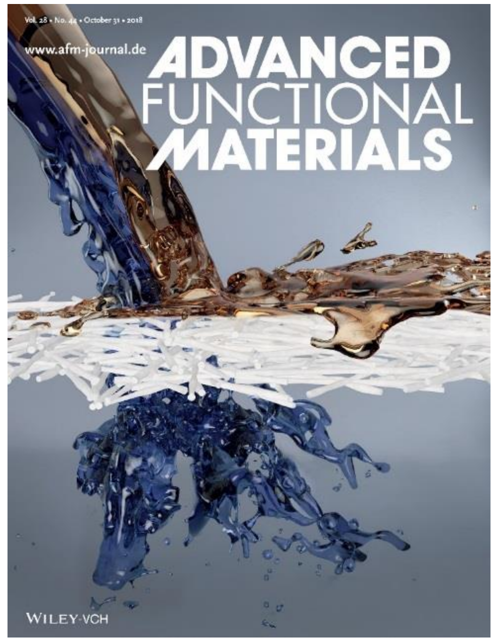
SOCIETAL CONTEXT & CHALLENGES



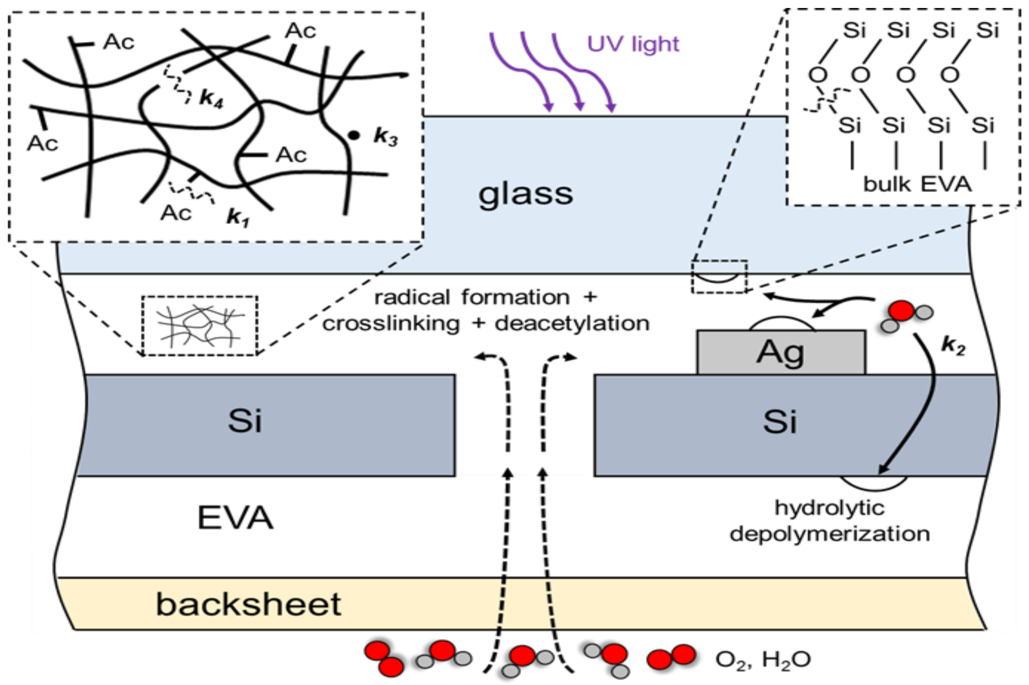
D'hooge, Guillaneuf *et al. Macromol. Rapid Commun.* **2018**, 39, 1800193

Zhao et al. ACS Appl. Mater. Interfaces. **2016**, 8, 14845

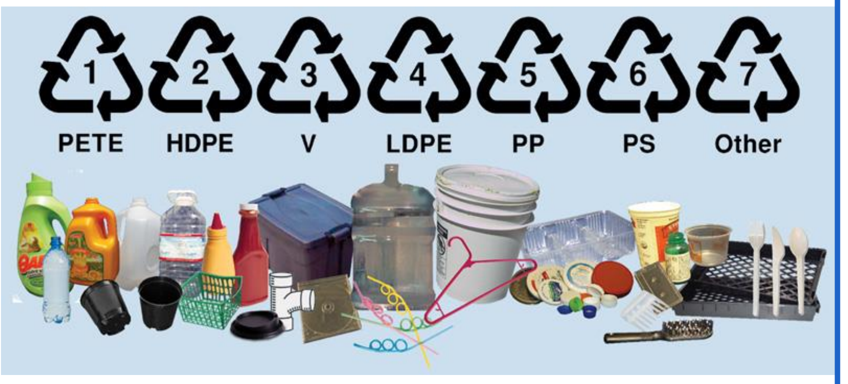




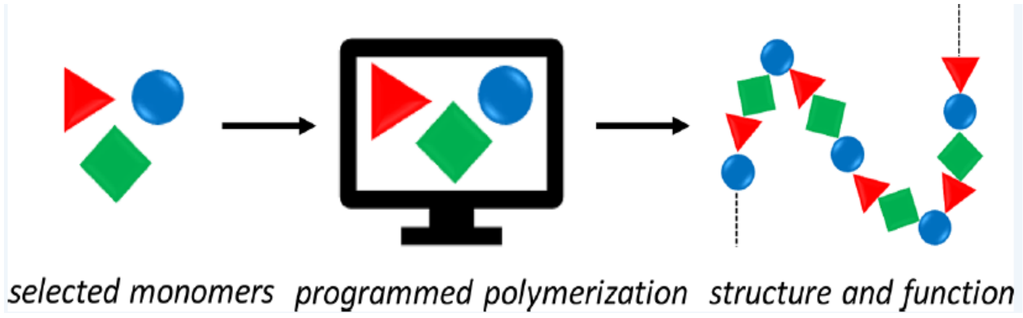
De Clerck, D'hooge *et al. Adv. Funct. Mater* ***2018****, 44, 1804138*



Tracy, D'hooge *et al. Prog. Photovoltaics.* **2018**, 26, 981

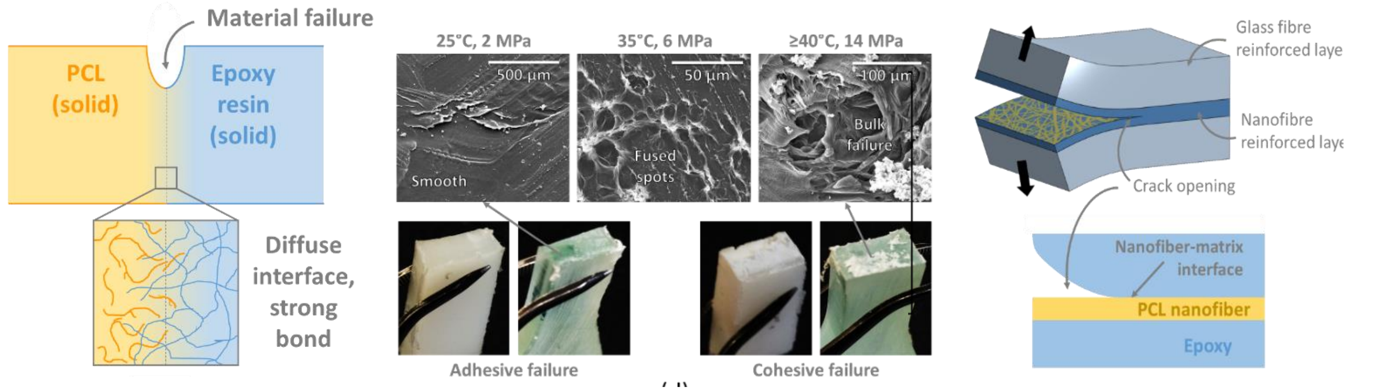


Fiorio, D'hooge *et al. Polymers* **2019**, 11, 25



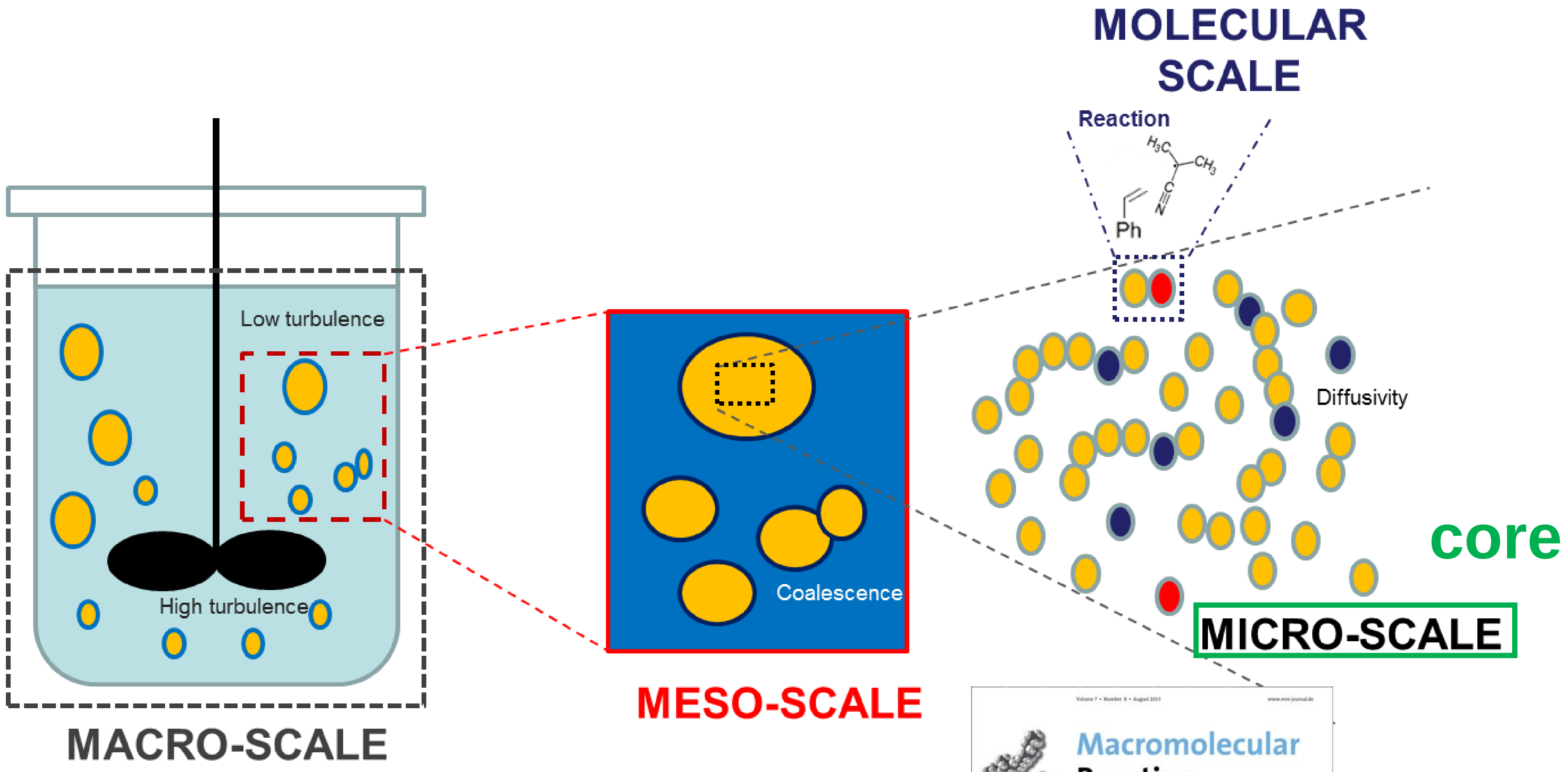
Szymanski *et al. Acc. Chem. Res.* **2018**, 51, 649

D'hooge, Lutz *et al*. Macromolecules **2016**, 49, 9336



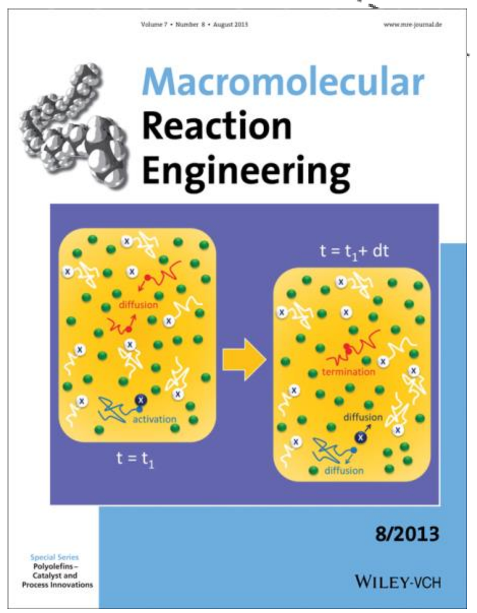
De Clerck, D'hooge *et al. Adv. Funct. Mater* **2019**, 44, 1807434

MULTI-SCALE CHARACTER OF POLYMERIZATION



D'hooge D.R. *et al. Prog. Polym. Sci.* **2016** 58, 59

Mastan *et al. Prog. Polym. Sci.* **2015**, 45, 71

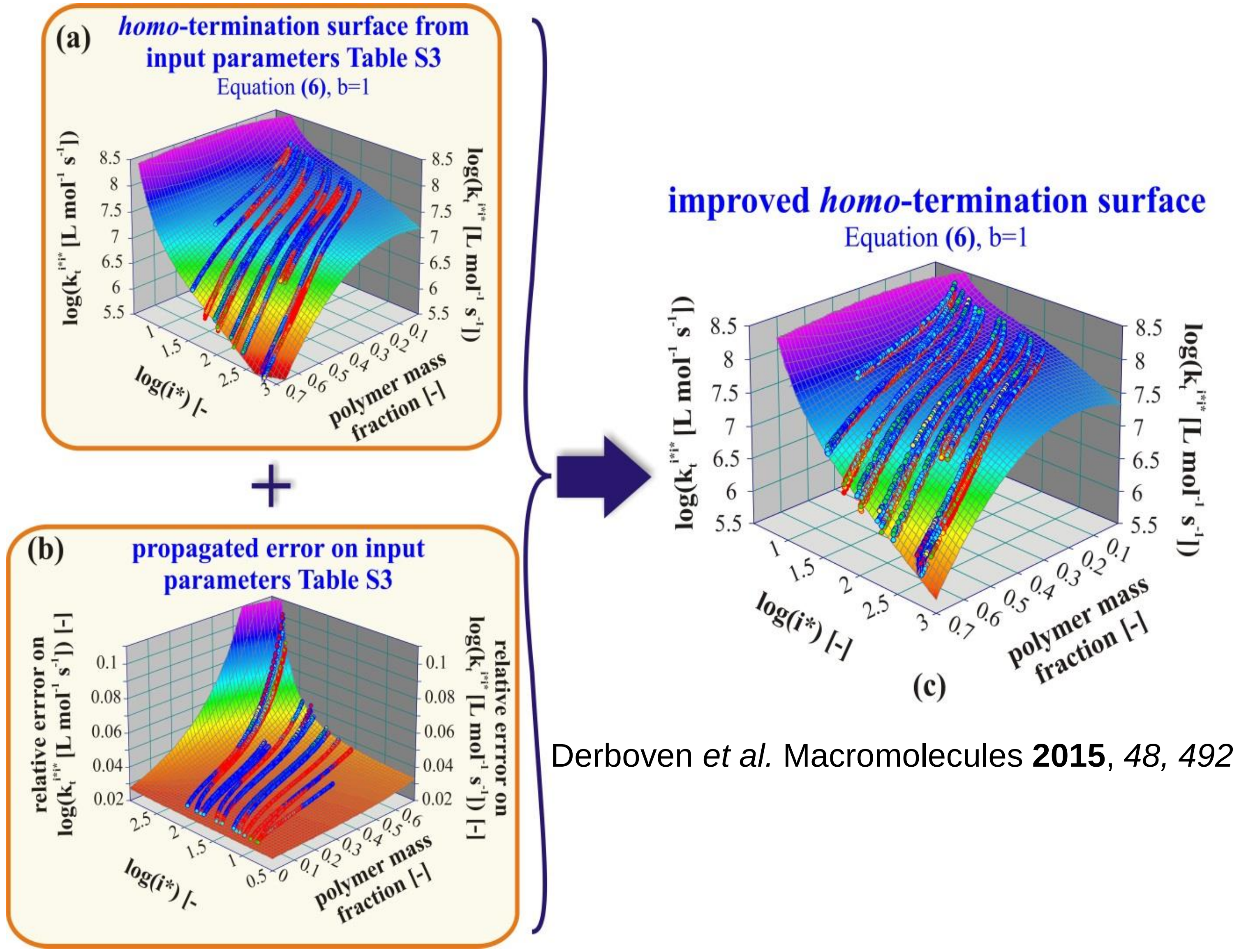


D'hooge *et al.* Macromol. React Eng. **2013**, *7, 362*

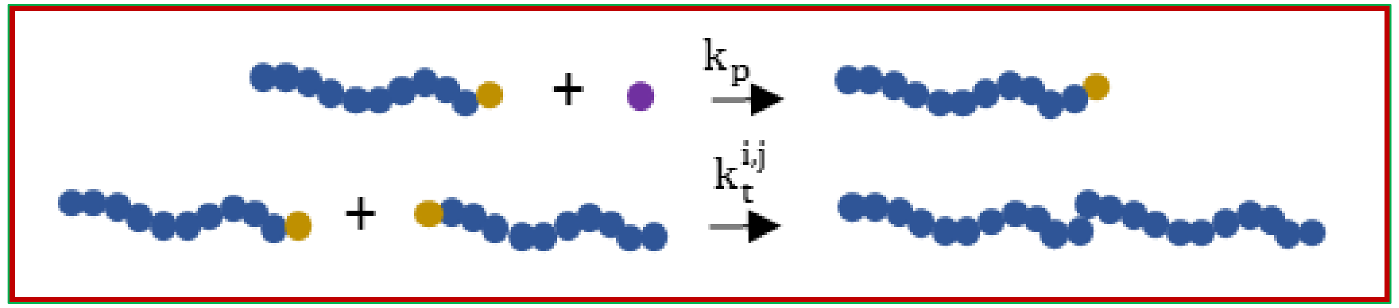
Peklak et al. J. Polym. Sc. Polym Chem/ **2006**, 44, 1071

Achilias and Kiparissides Macromolecules **1992**, *25, 3739*

$$A + B \underset{k_{-diff}}{\overset{k_{+diff}}{\rightleftarrows}} AB \xrightarrow{k_{chem}} C \Leftrightarrow A + B \xrightarrow{k_{app}} C$$

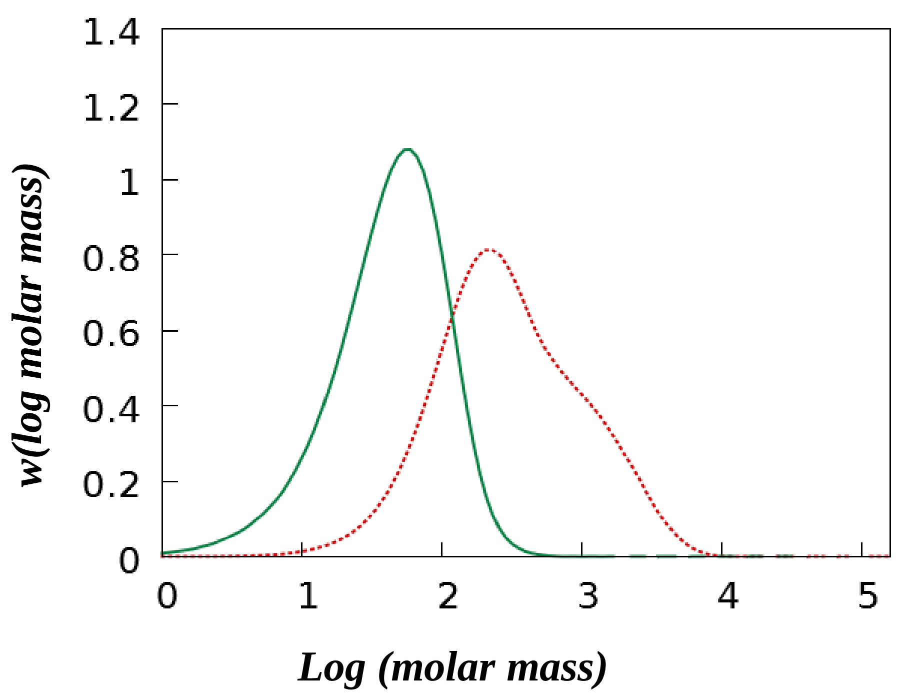


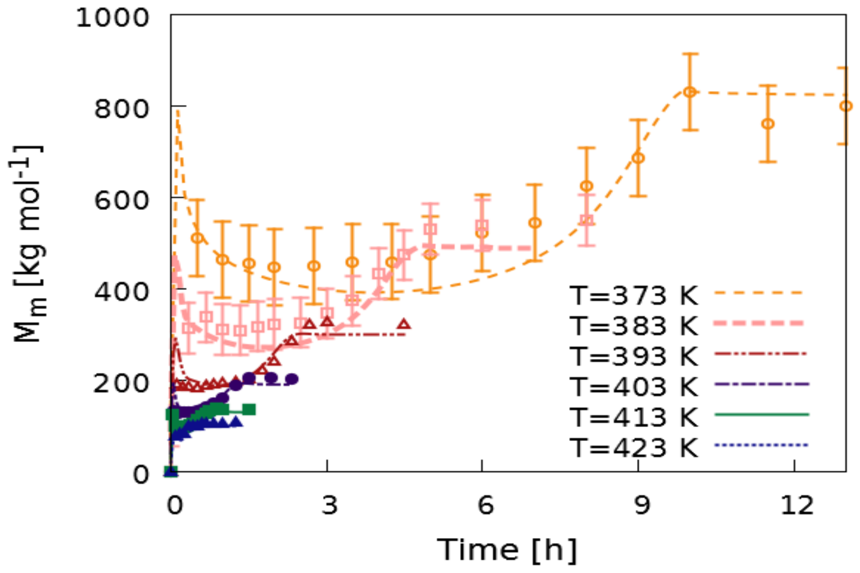
Derboven *et al.* Macromolecules **2015**, *48, 492*



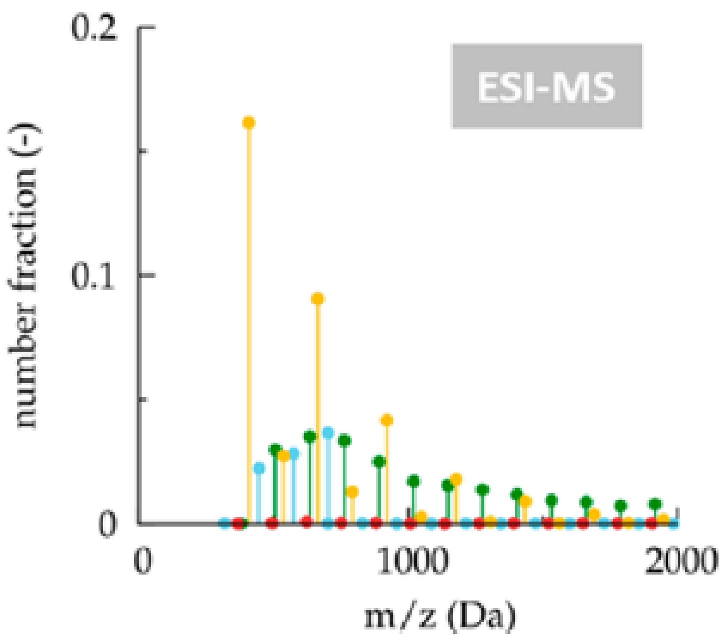
MICRO-SCALE: SYNERGY MODEL AND EXPERIMENT

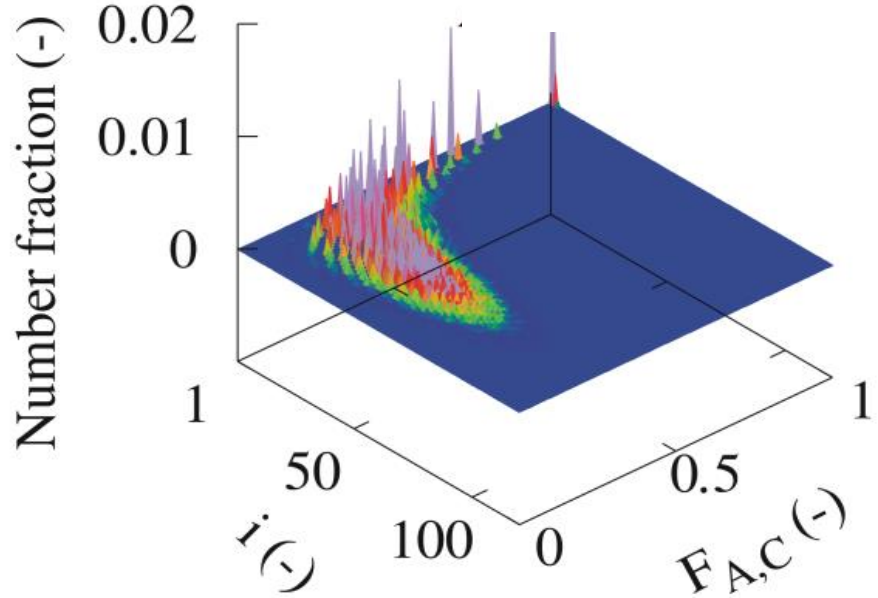
Generation 1



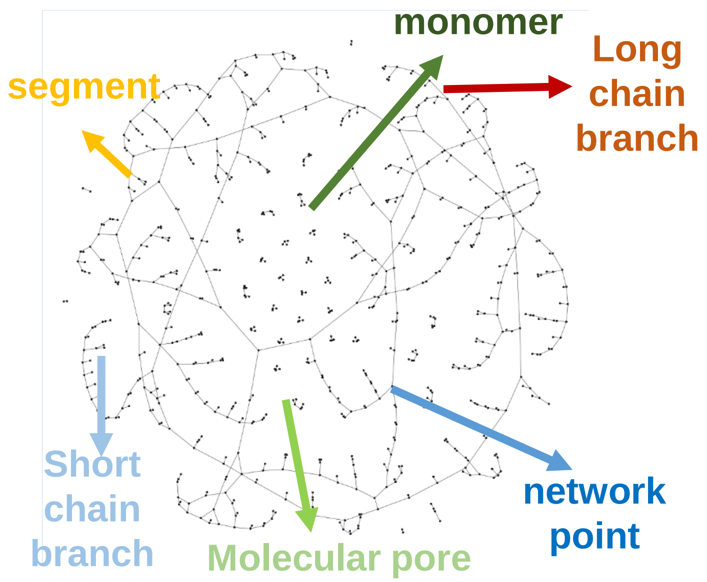


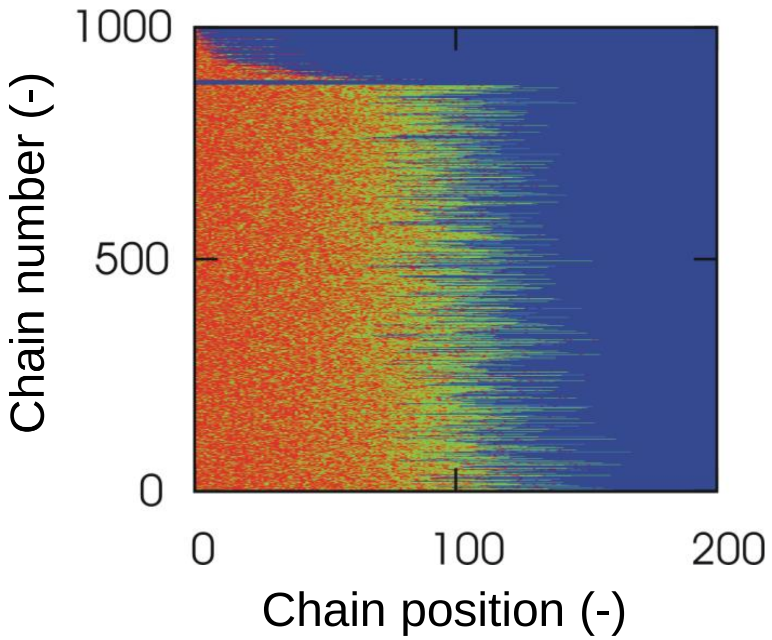
Generation 2

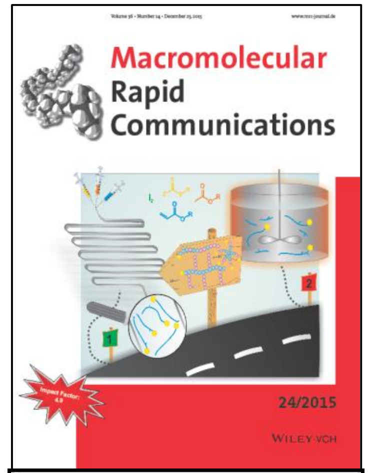


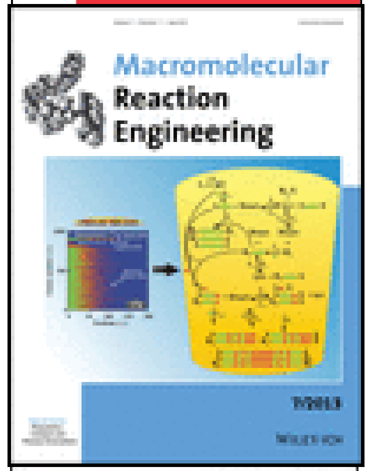


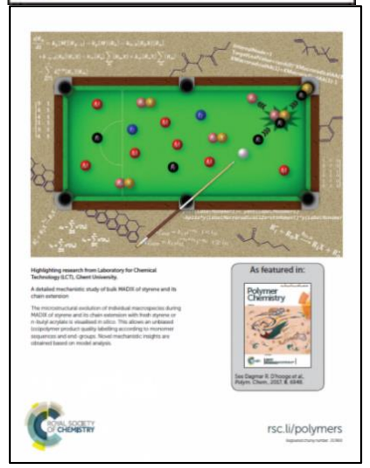
Generation 3









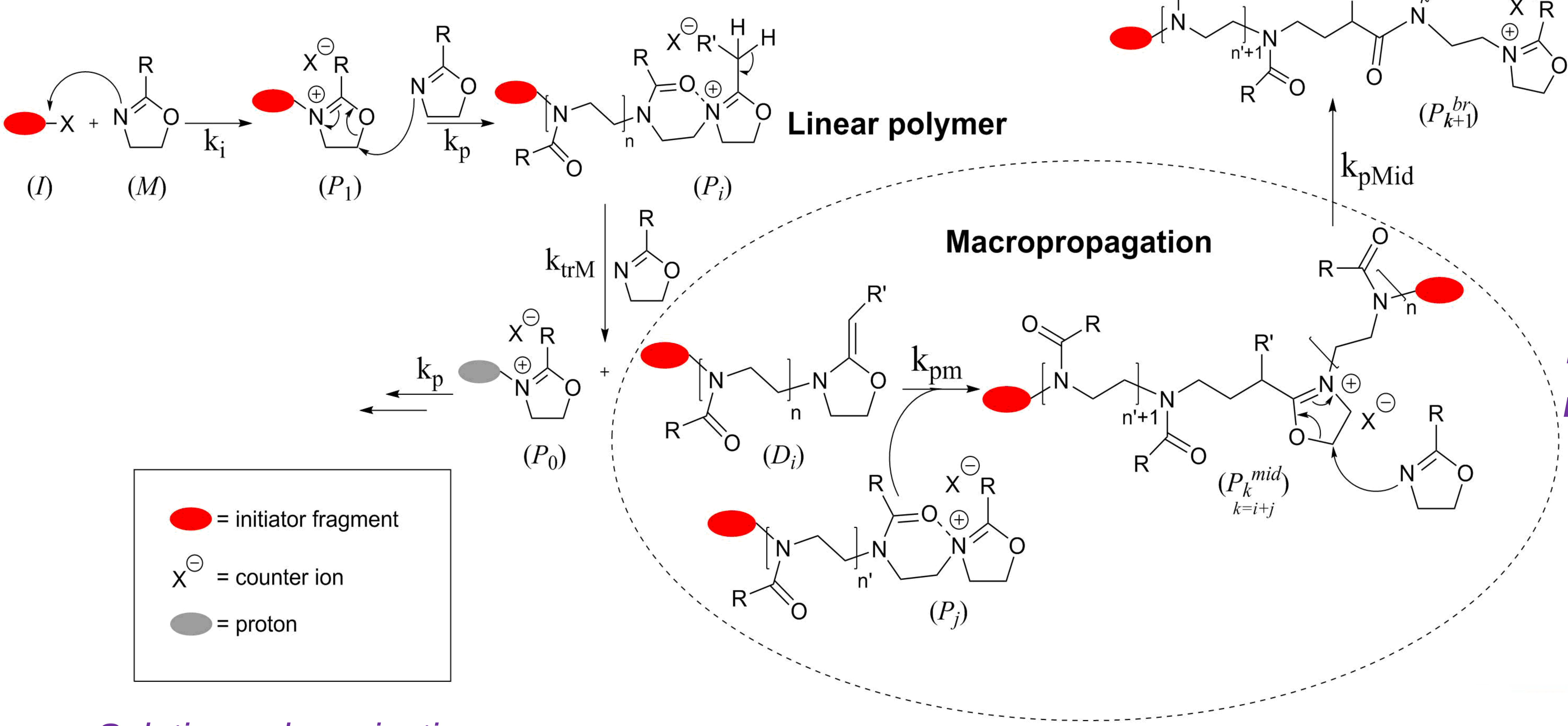


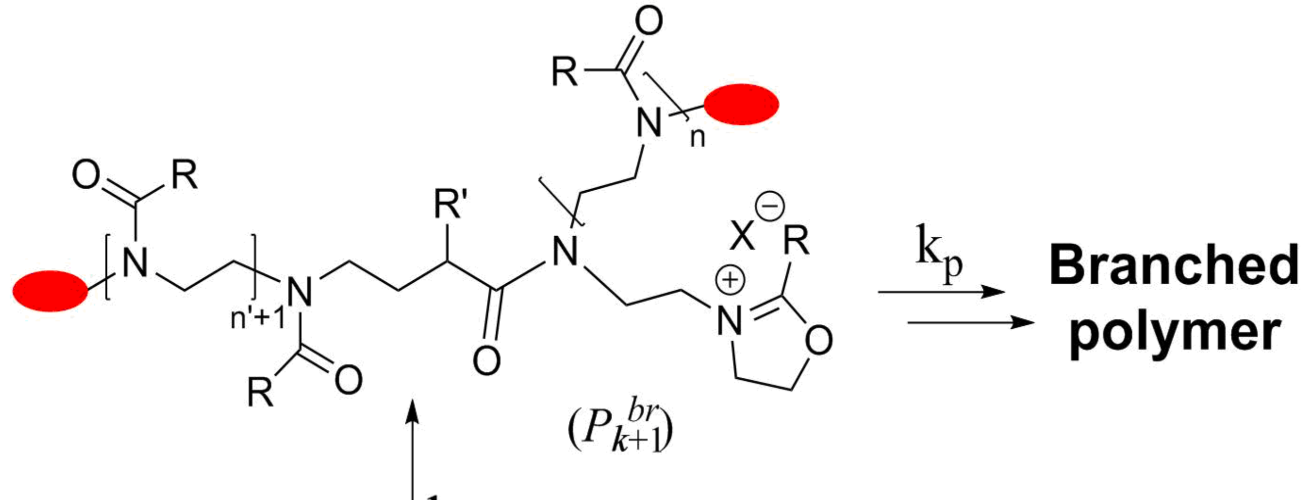
Complexity and macromolecular structural detail

Van Steenberge P.H.M. *et al. Macromolecules* **2011**, 44, 8716; Van Steenberge P.H.M. *et al. Macromolecules* **2012**, 45, 8519.; Van Steenberge P.H.M. *et al. Chem. Eng. Sci.* 2014, 11, 185; D'hooge D.R. *et al. Polym. Chem.* **2015**, 6, 7081; Derboven P. *et al. Macromol. Rapid Commun.* **2015**, 36, 2149; D'hooge D.R. *et al. Prog. Polym. Sci.* **2016**, 58, 59; Devlaminck D.J.G. *et al. Polym. Chem.* **2017**, 8, 6948

CATIONIC RING-OPENING POLYMERIZATION OF 2-OXAZOLINES

Ideally only chain initiation and propagation





Limited research on side reactions and associated rate coefficients

Solution polymerization

⬇

Main focus on chemistry

OUTLINE

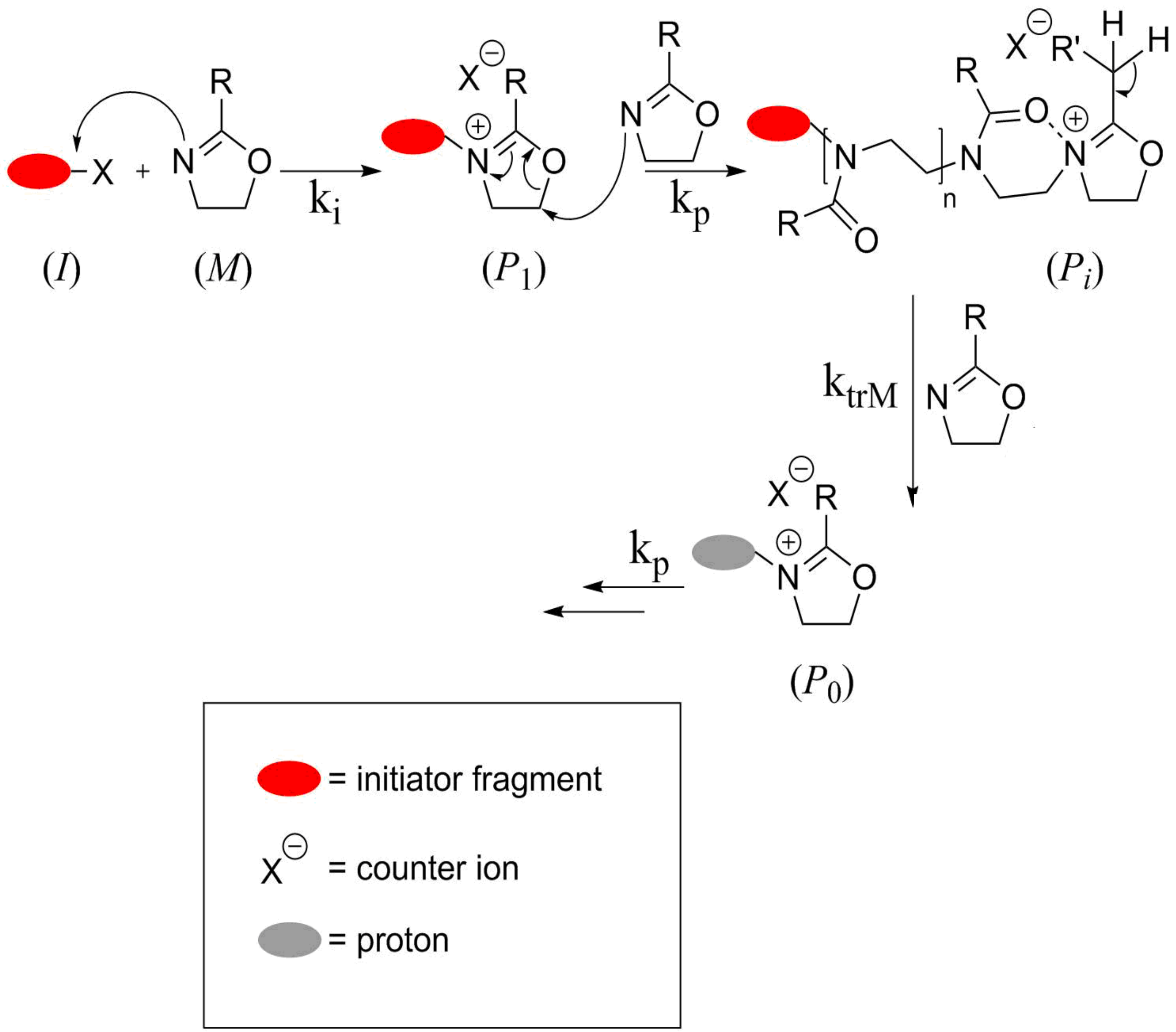
1. Homopolymerization
    - Chain initiation and propagation reactivity
    - Chain transfer to monomer reactivity
    - Macropropagation reactivity

Van Steenberge *et al*. *Macromolecules* **2015**, 48, 7765
Glassner *et al. Eur. Polym. J.*, **2015**, 65, 298
Van Steenberge *et al*. *Nat. Commun.* **2019**, to be subm.
Arraez *et al*. *Macromolecules* **2019**, to be submitted

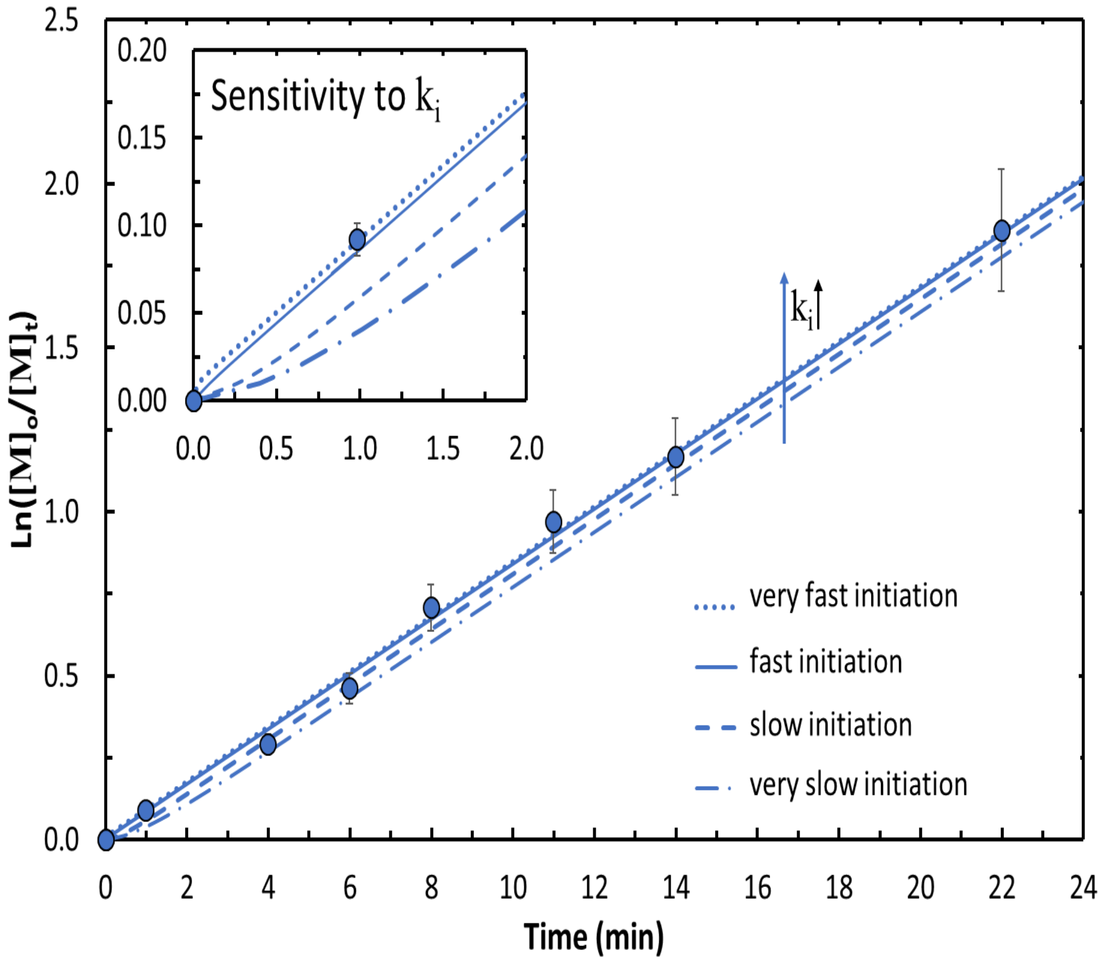
2. Copolymerization with functional comonomer in view of therapeutics & hydrogels
    - Unbiased qualification tool for evaluation functionalization success
    - Design of chemical structure of the comonomers and reaction conditions
    - Applicability for low and high target degrees of polymerization (target DPs)

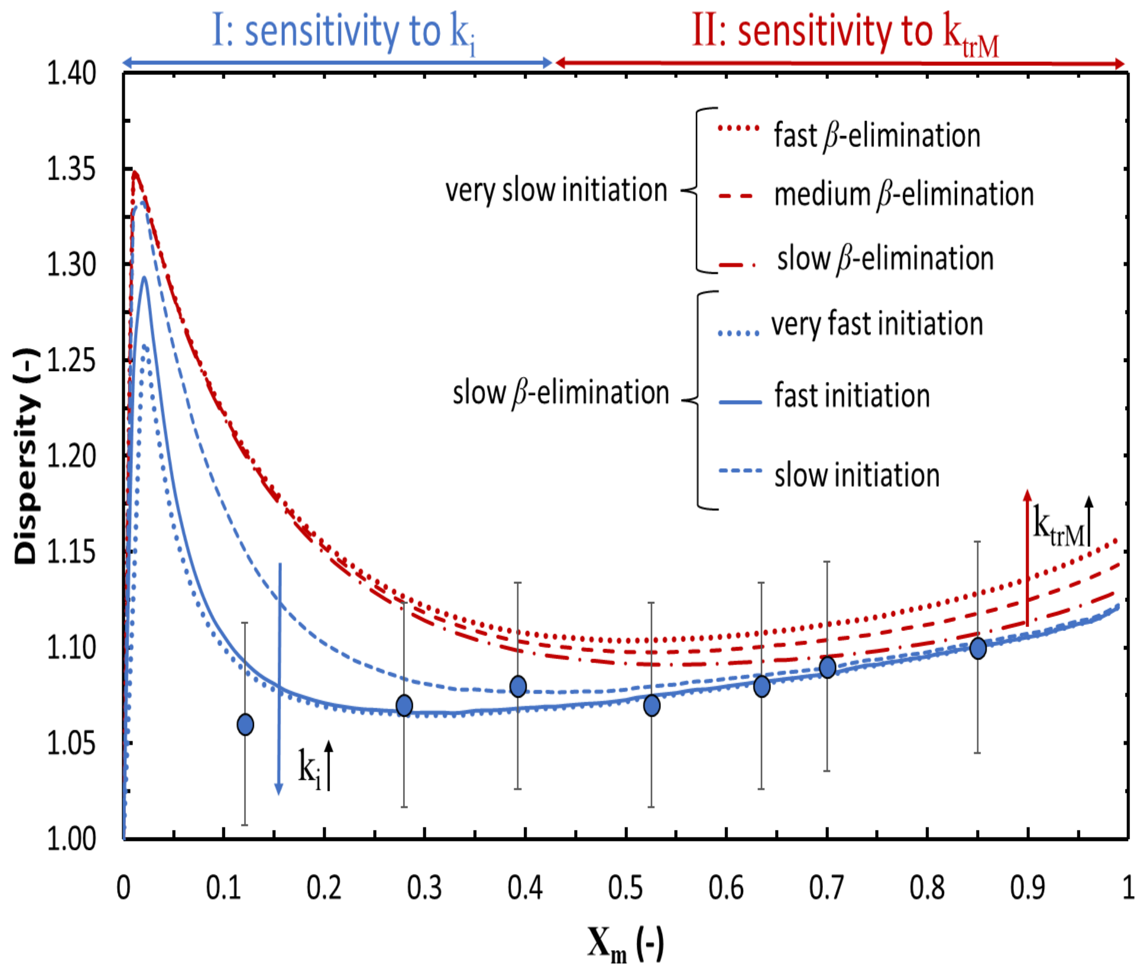
Van Steenberge *et al*. *Macromolecules* **2015**, 48, 7765
Van Steenberge *et al*. *Nat. Commun.* **2019**, to be subm.

WHICH EXPERIMENTAL RESPONSES ?



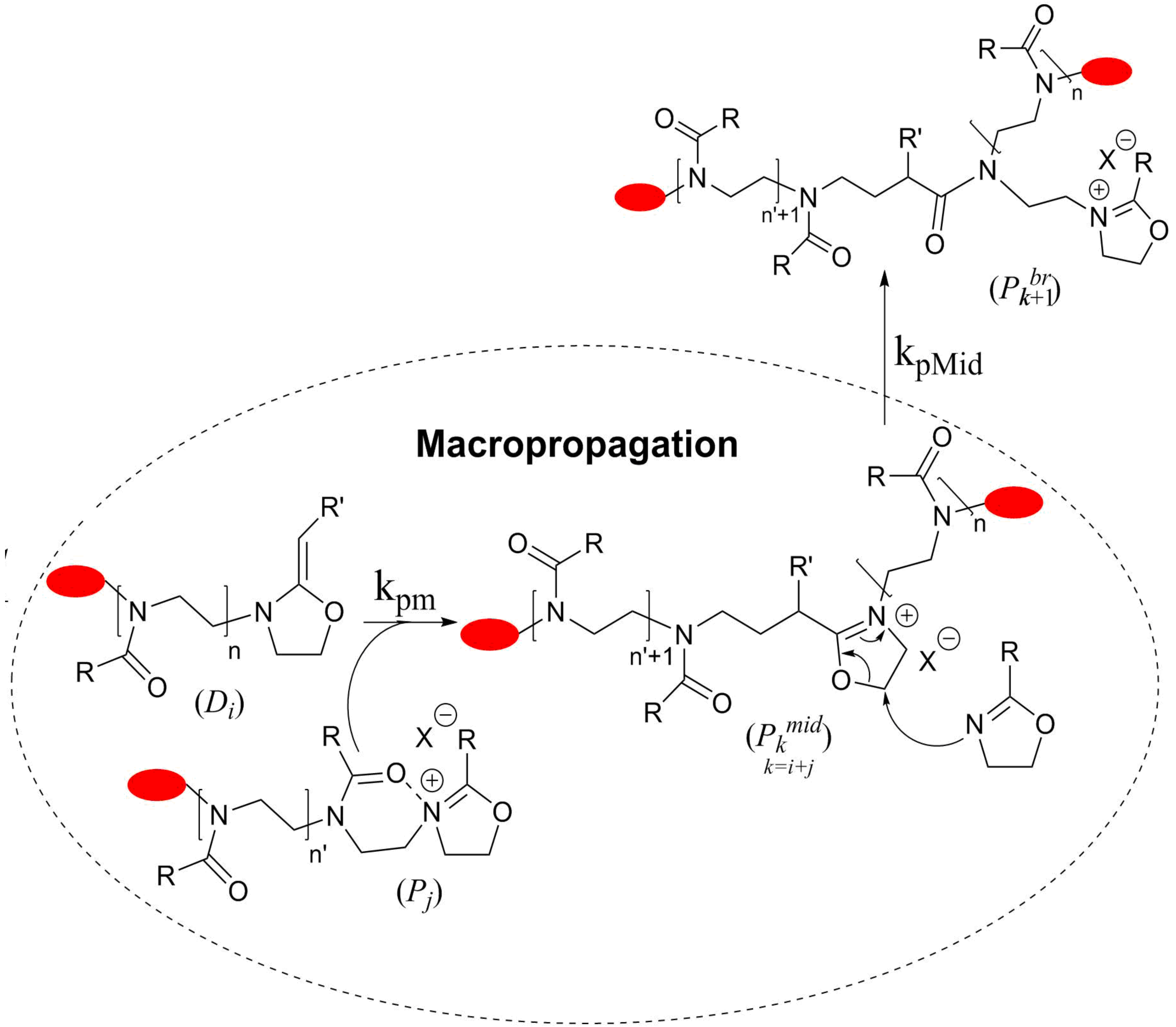
CROP of EtOx ($[M]_o$ = 4 mol·L^{-1}; target DP of 100; acetonitrile; 393 K

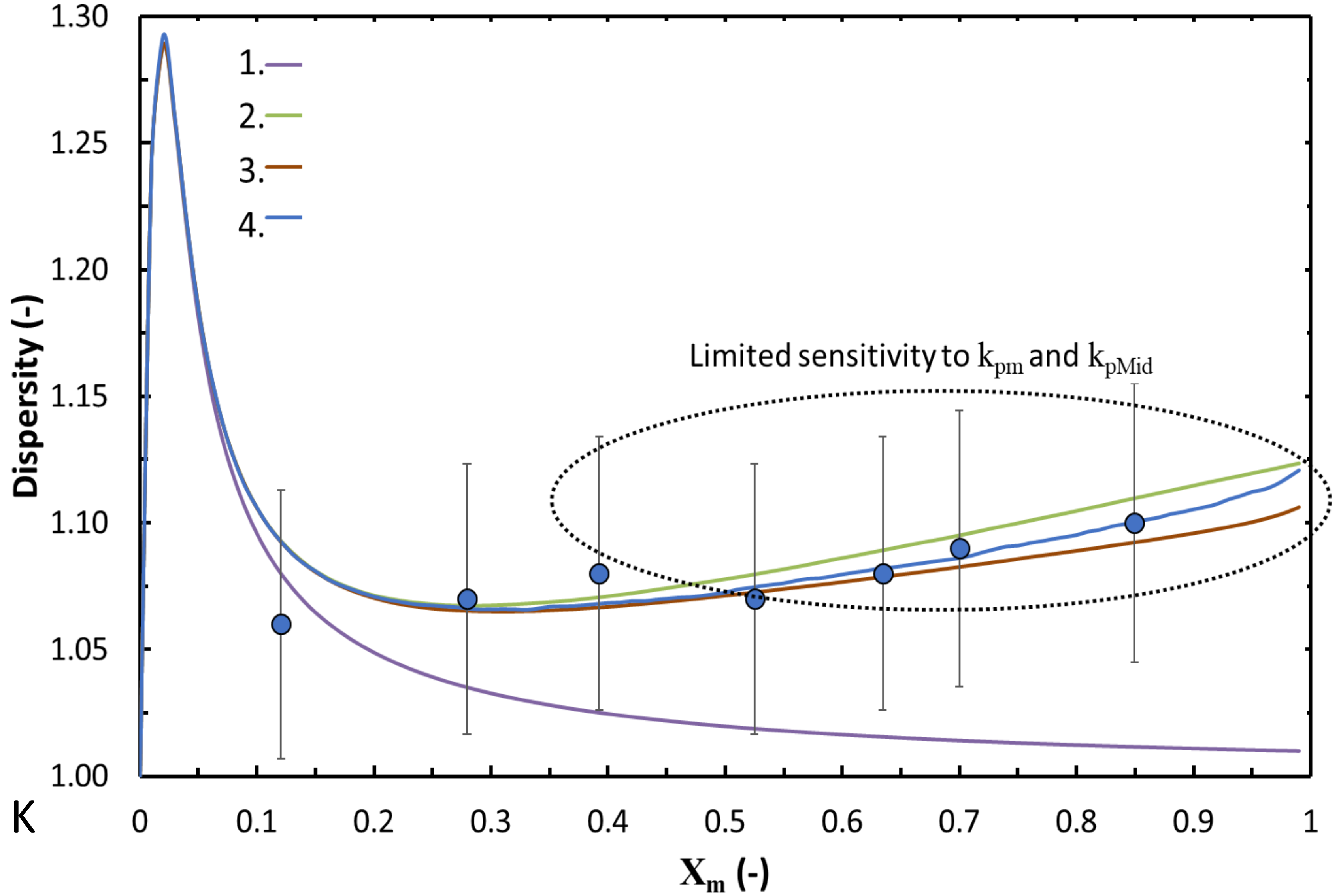




WHICH EXPERIMENTAL RESPONSES ?

	k_{trM} (L·mol^{-1}·s^{-1})	k_{pm} (L·mol^{-1}·s^{-1})	k_{pMid} (L·mol^{-1}·s^{-1})
1.	✖	✖	✖
2.	✓ 6.57×10^{-2}	✖	✖
3.	✓ 6.57×10^{-2}	✓ 6.99×10^{-2}	✖
4.	✓ 6.57×10^{-2}	✓ 6.99×10^{-2} ×0.1	✓ 3.49×10^{-2}
5.	✓ 6.57×10^{-2}	✓ 6.99×10^{-3}	✓ 3.49×10^{-2} ×10
6.	✓ 6.57×10^{-2}	✓ 6.99×10^{-3}	✓ 3.49×10^{-1}
● / ---	Experimental		

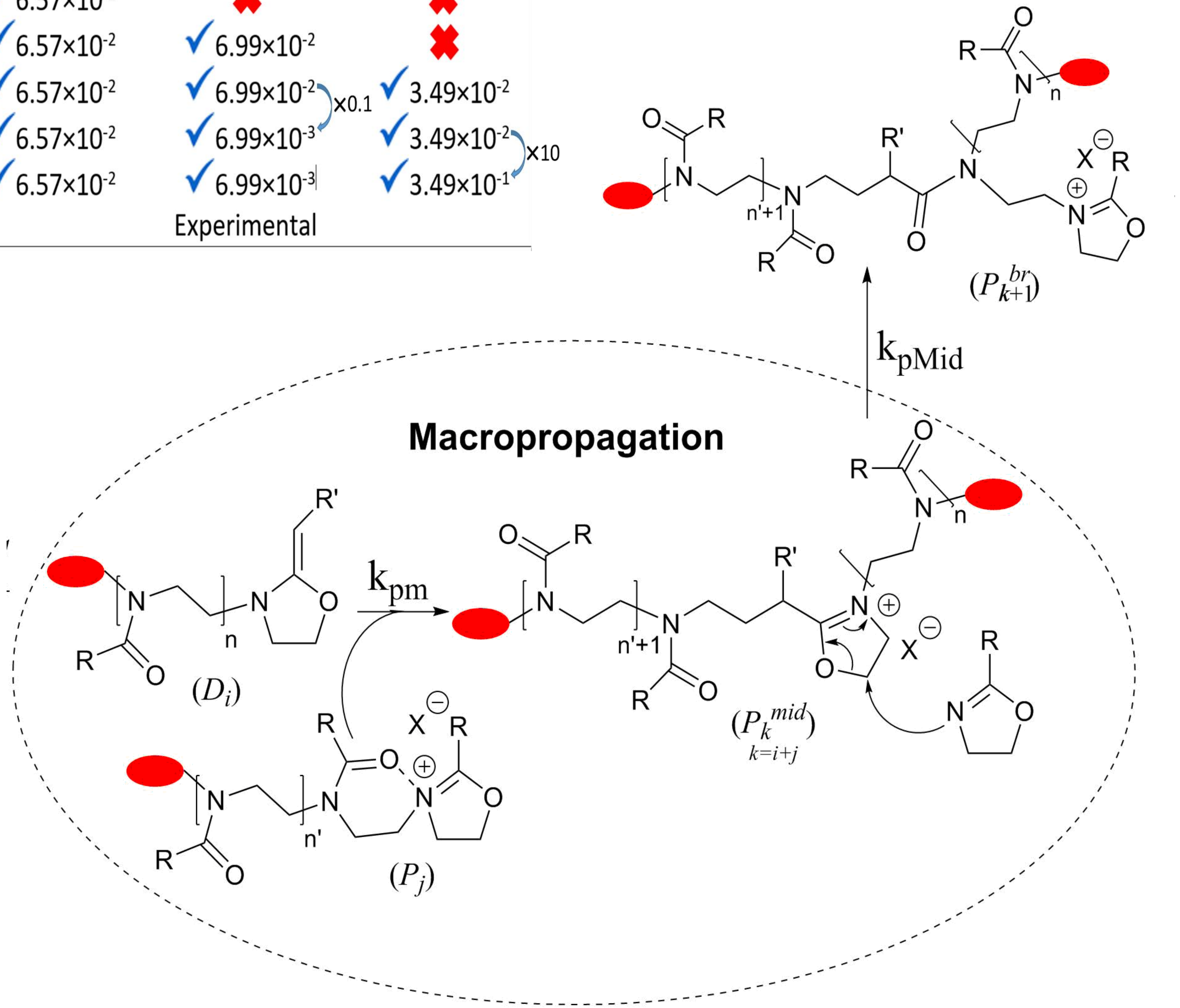


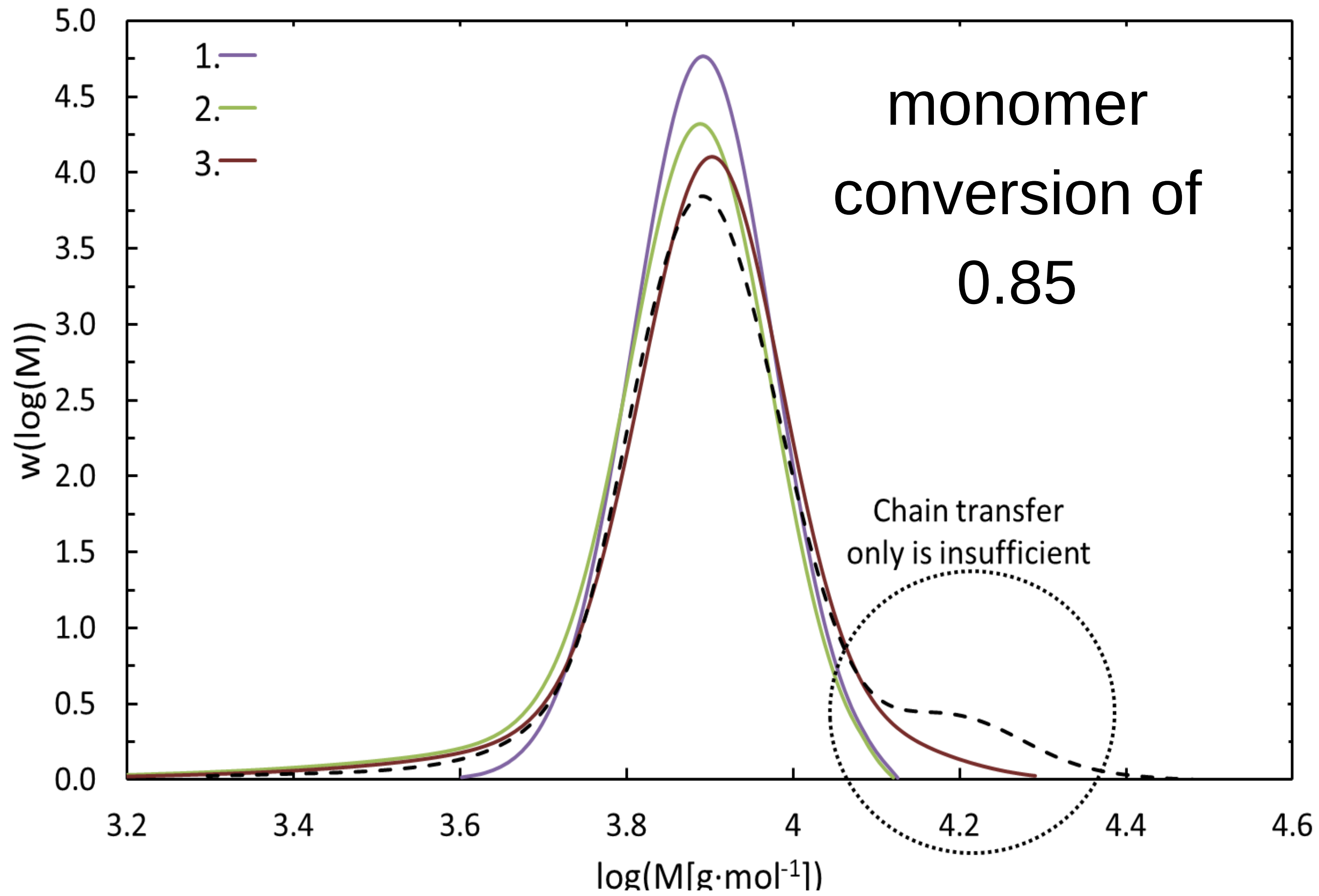


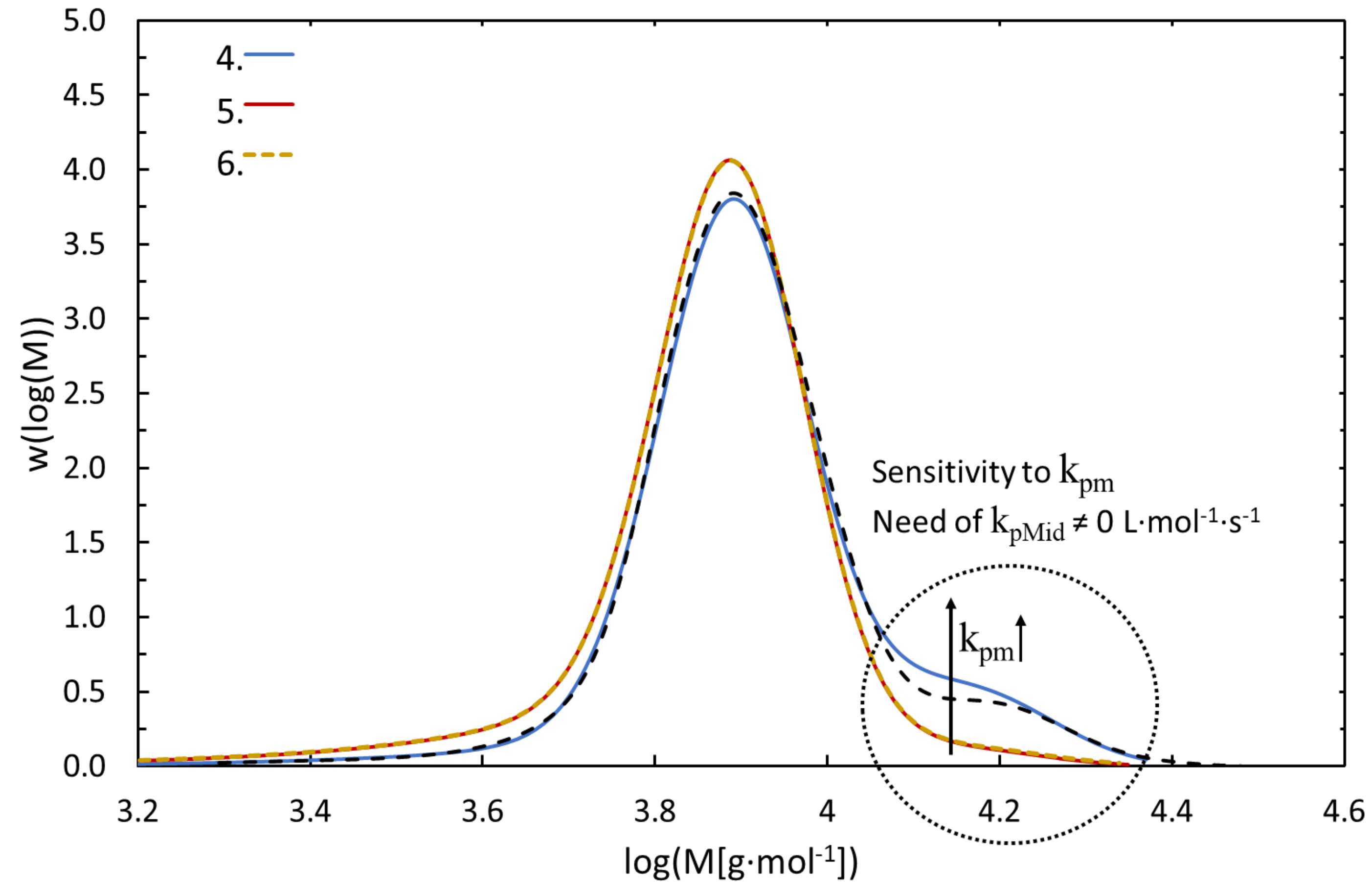
CROP of EtOx ($[M]_o$ = 4 mol·L^{-1}; target DP of 100; acetonitrile; 393 K

WHICH EXPERIMENTAL RESPONSES ?

	k_{trM} (L·mol⁻¹·s⁻¹)	k_{pm} (L·mol⁻¹·s⁻¹)	k_{pMid} (L·mol⁻¹·s⁻¹)
1.	✖	✖	✖
2.	✔ 6.57×10^{-2}	✖	✖
3.	✔ 6.57×10^{-2}	✔ 6.99×10^{-2}	✖
4.	✔ 6.57×10^{-2}	✔ 6.99×10^{-2}	✔ 3.49×10^{-2}
5.	✔ 6.57×10^{-2}	✔ 6.99×10^{-3} ×0.1	✔ 3.49×10^{-2}
6.	✔ 6.57×10^{-2}	✔ 6.99×10^{-3}	✔ 3.49×10^{-1} ×10
● - - -		Experimental	



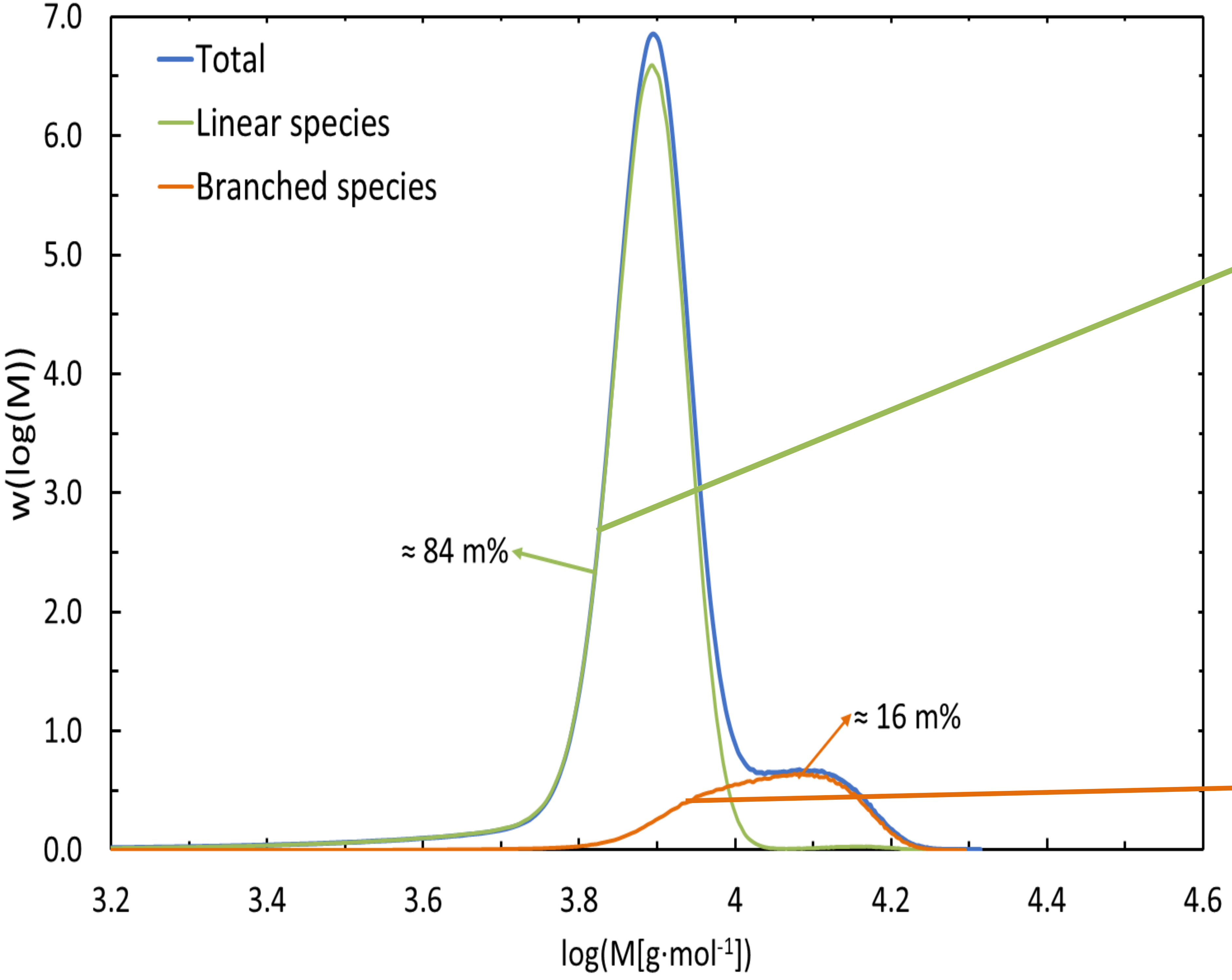




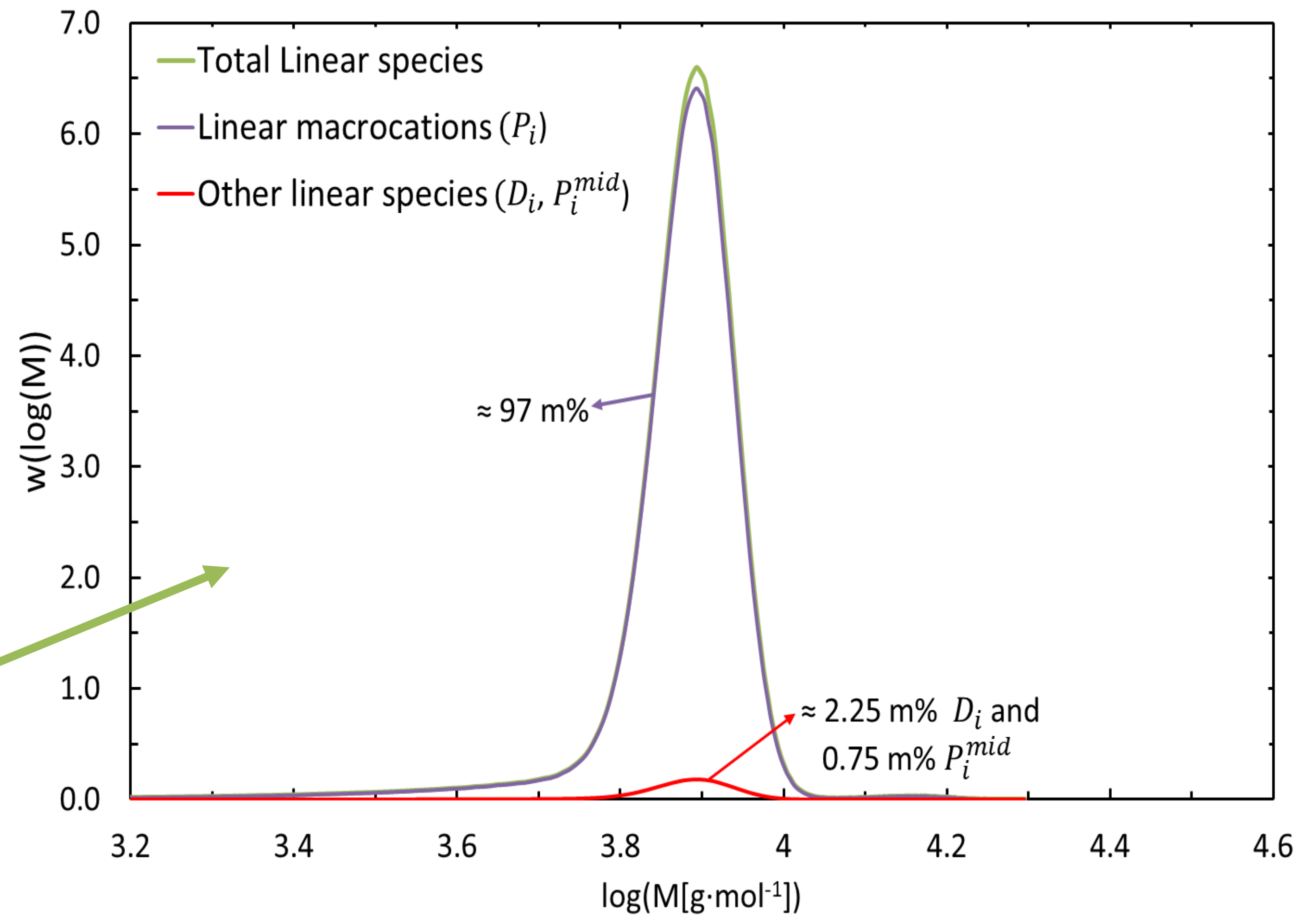
Correction for SEC broadening and topology difference

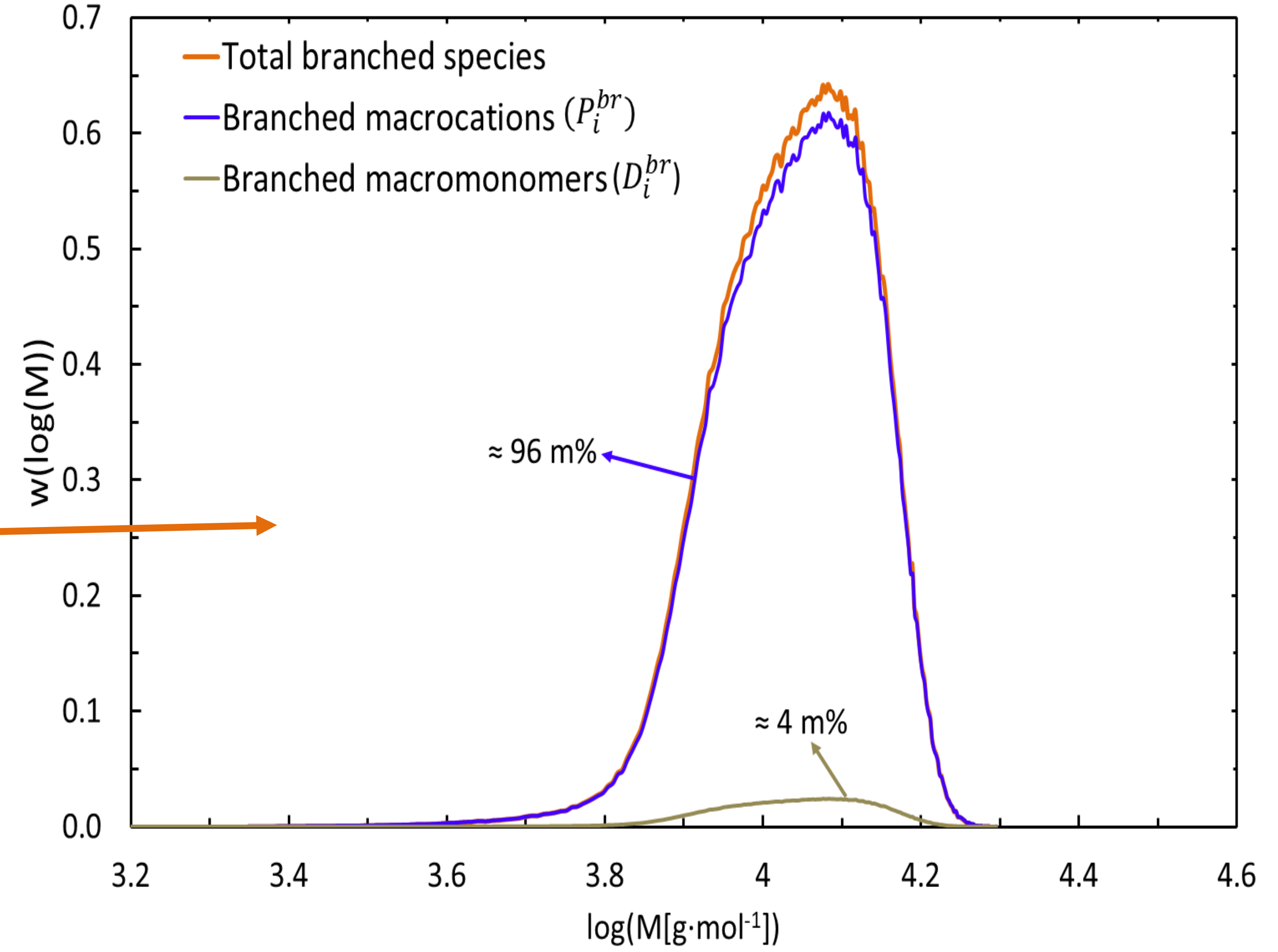
EXTRA INFORMATION BY MODELING

Differentiation according to topology

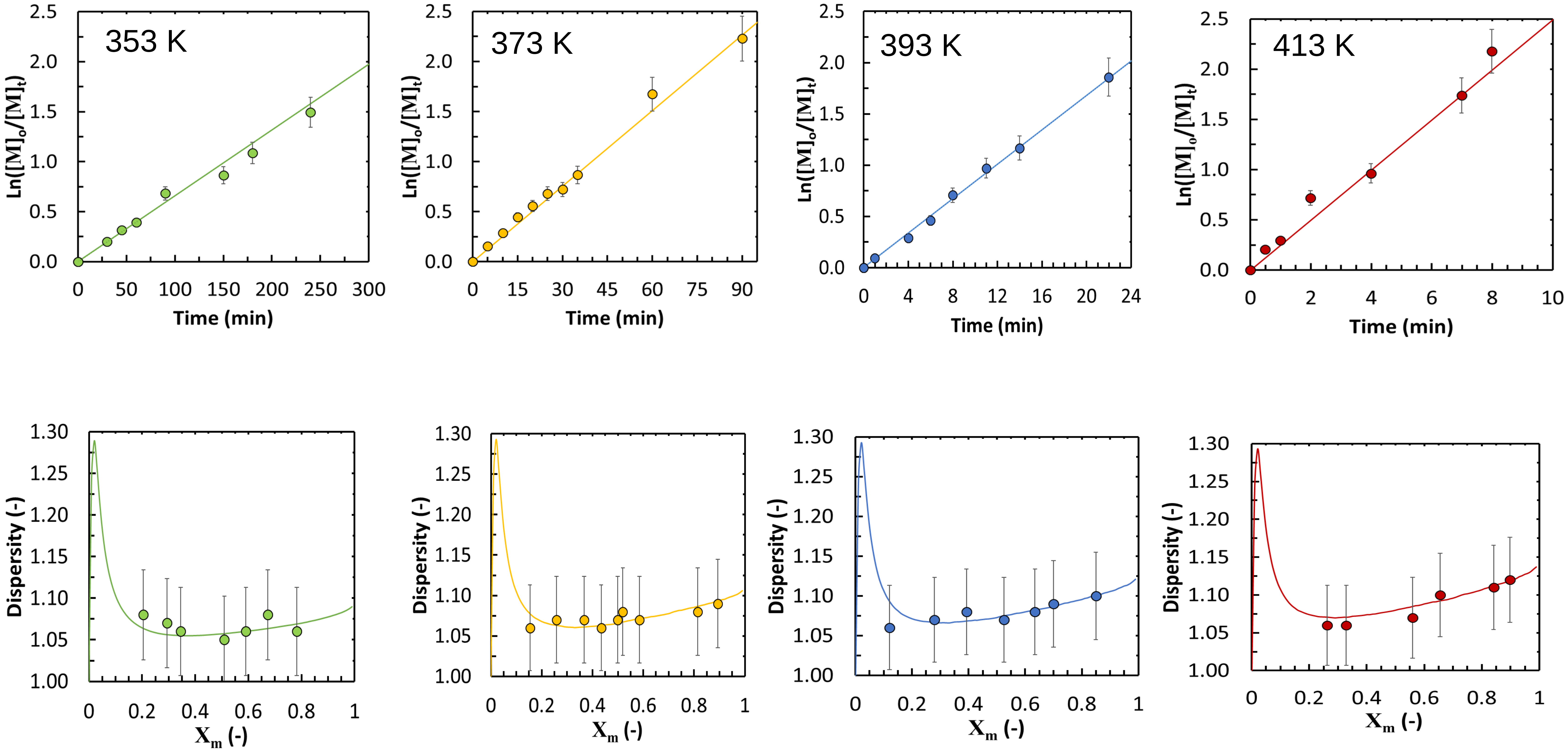


Absolute SEC traces accessible





SAME PROCEDURE (T) TO OBTAIN ARRHENIUS PARAMETERS



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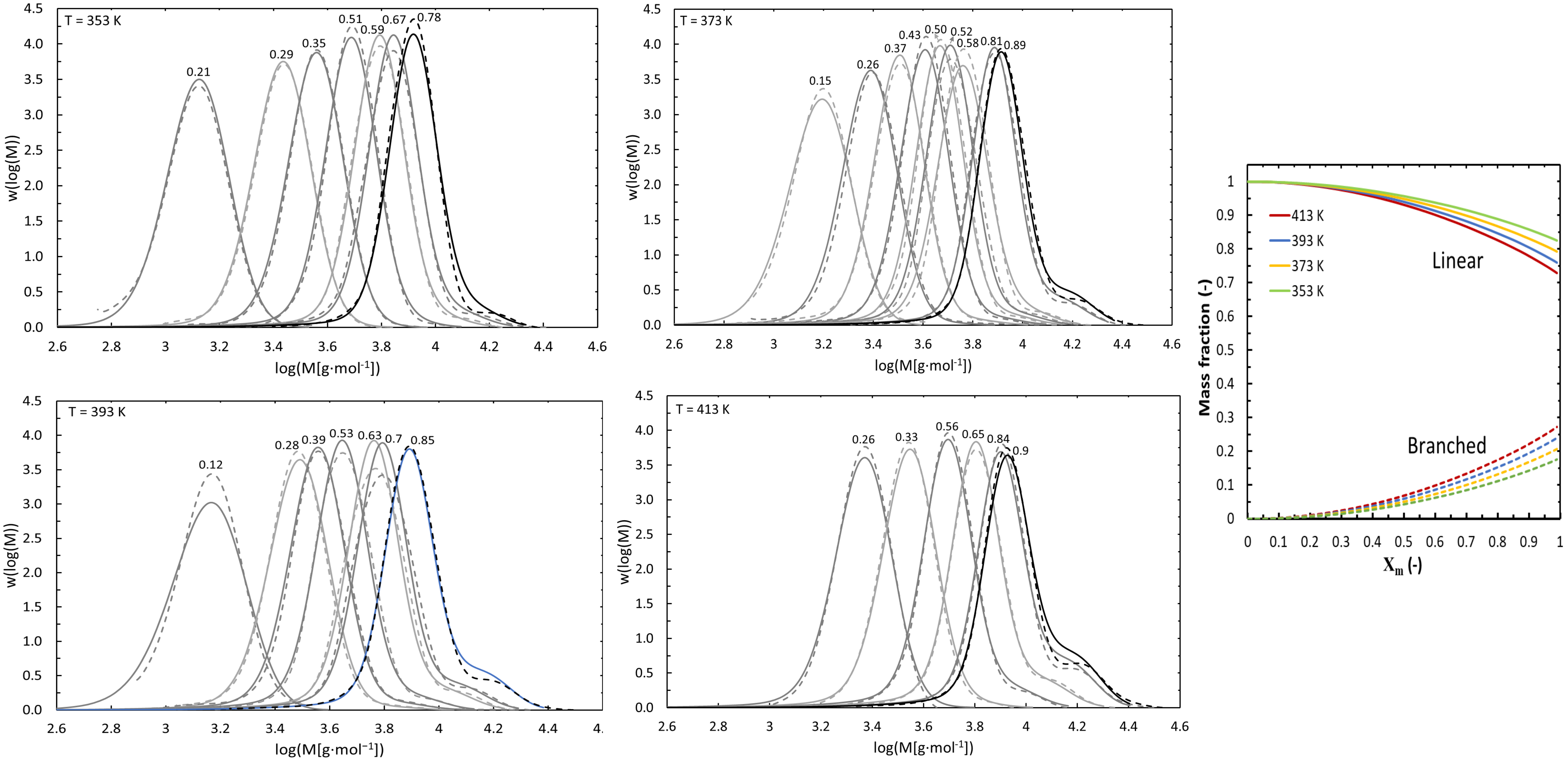
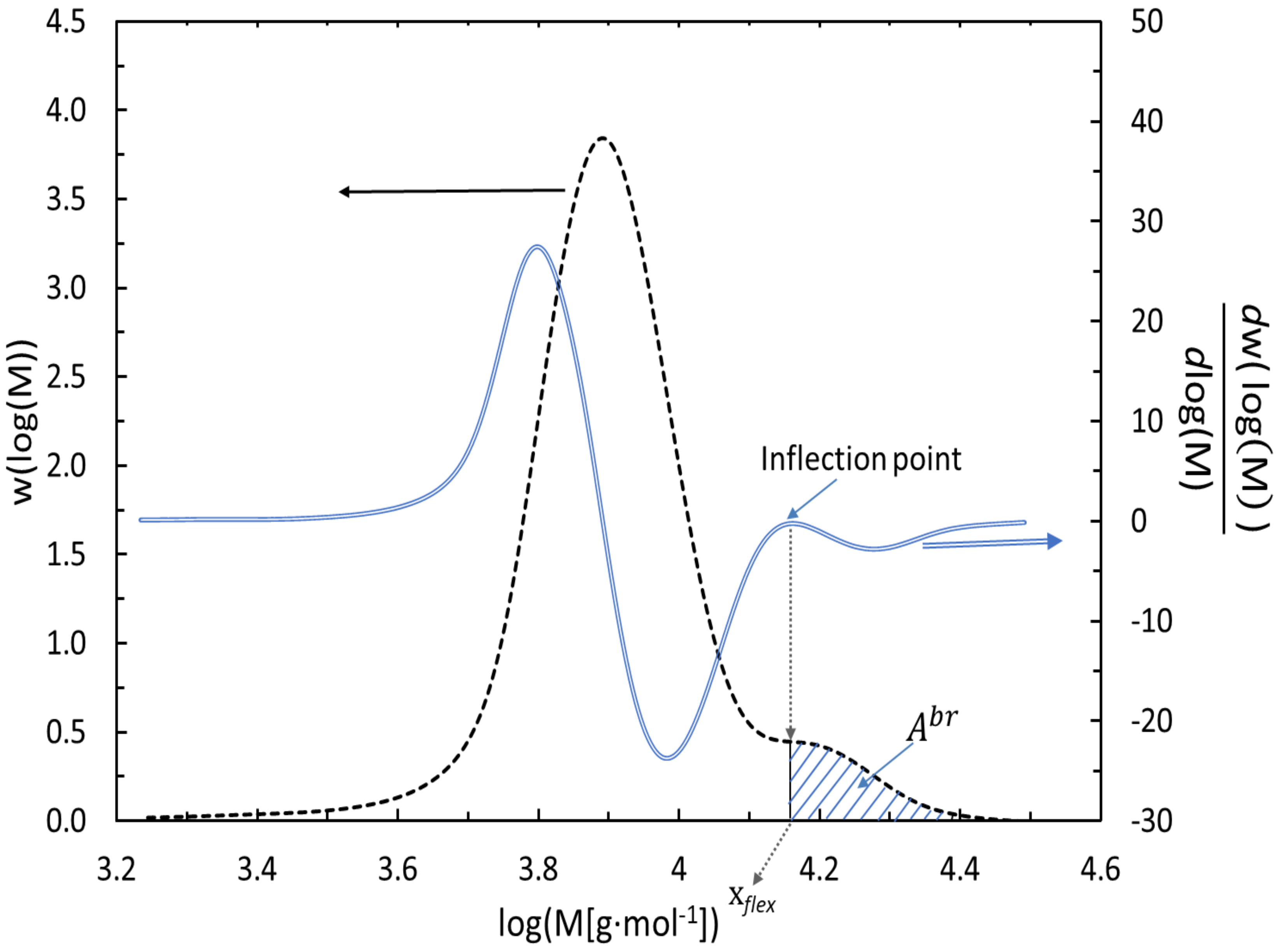
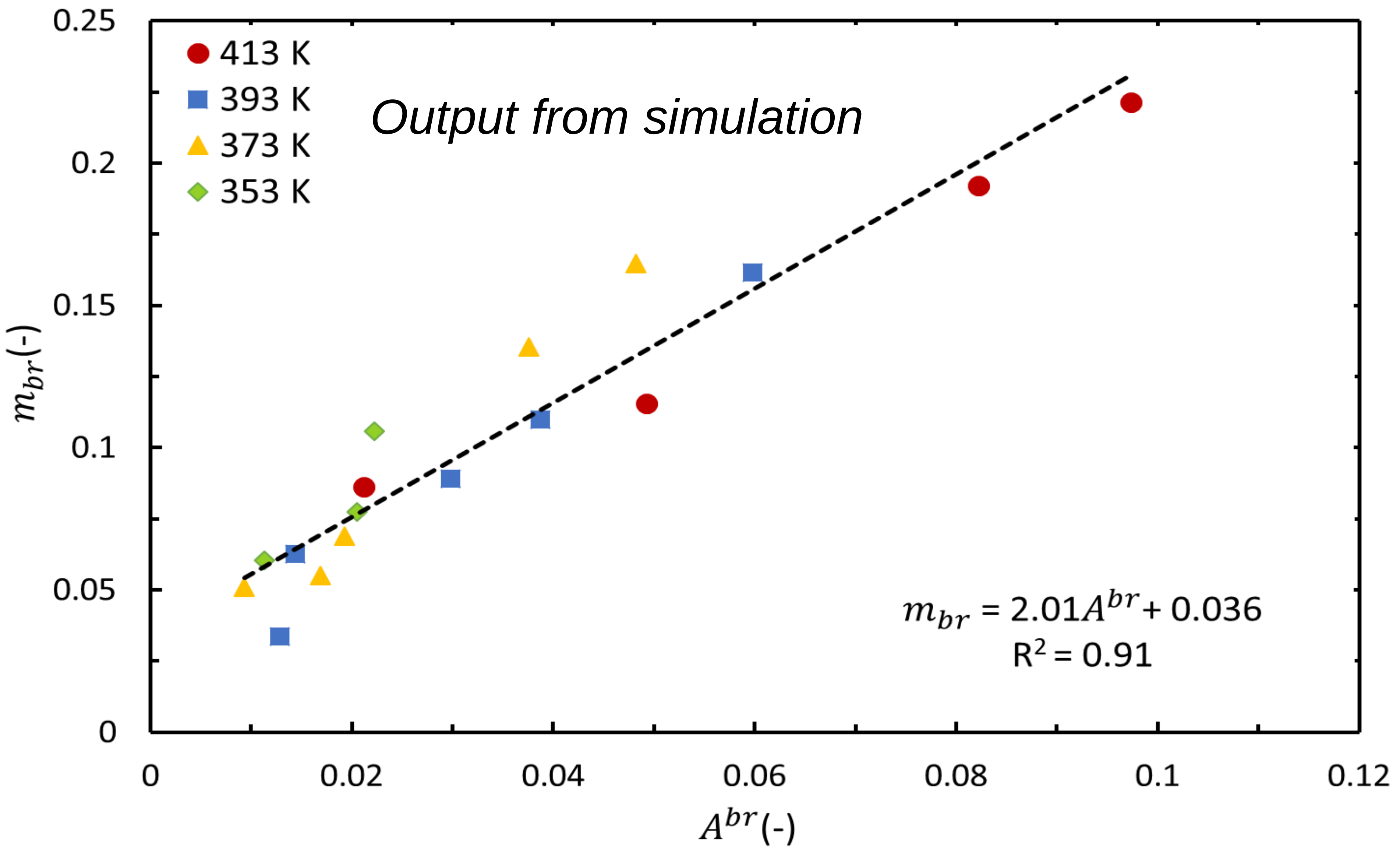


REVERSE ENGINEERING: DIRECT EXPERIMENTAL ANALYSIS ?

Linear calibration curve** to assess the **importance of branched species





Input from experimental SEC trace

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Glassner *et al. Eur. Polym. J.*, **2015**, 65, 298
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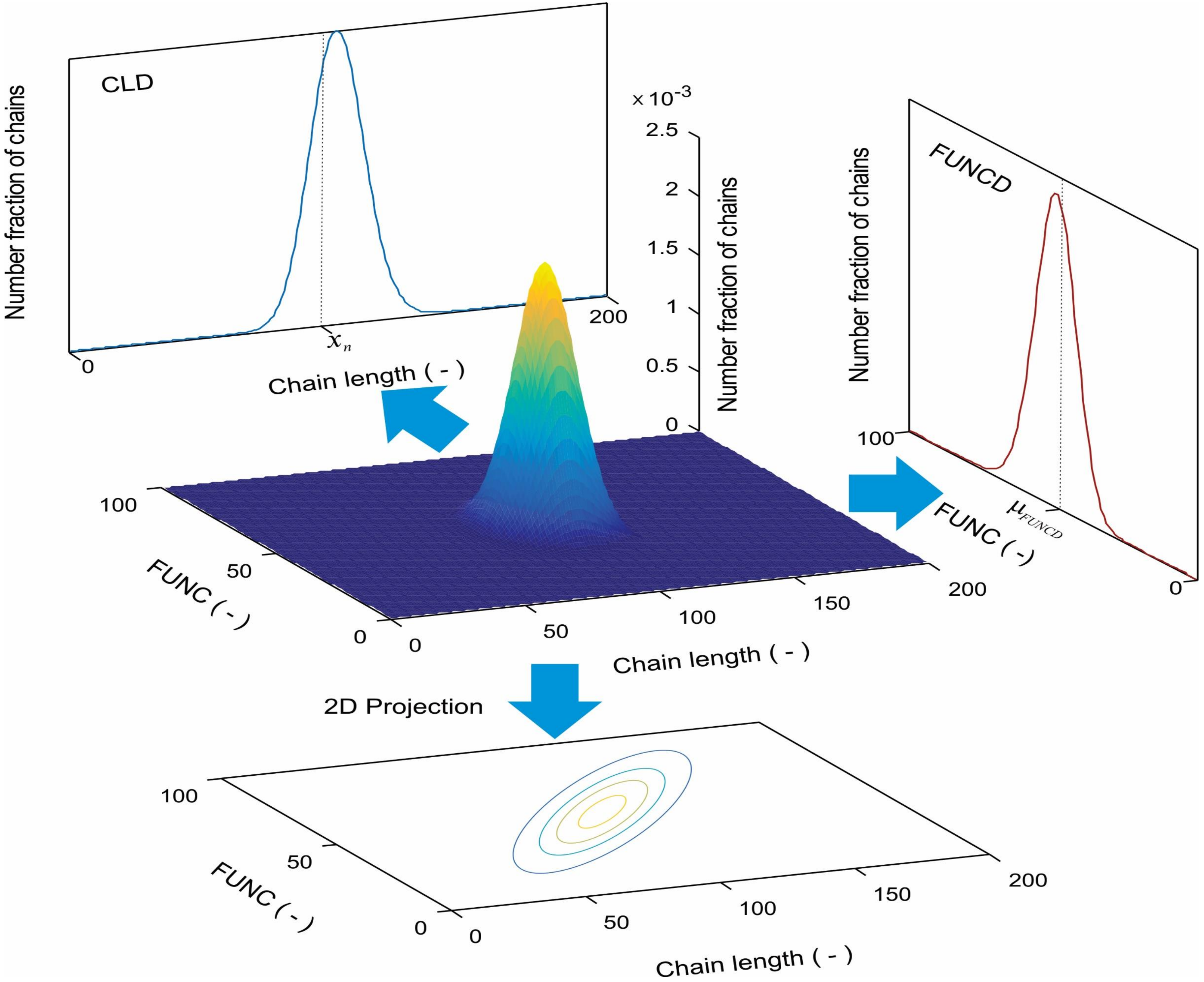
   - Unbiased qualification tool for evaluation functionalization success
   - Design of chemical structure of the comonomers and reaction conditions
   - Applicability for low and high target degrees of polymerization (target DPs)

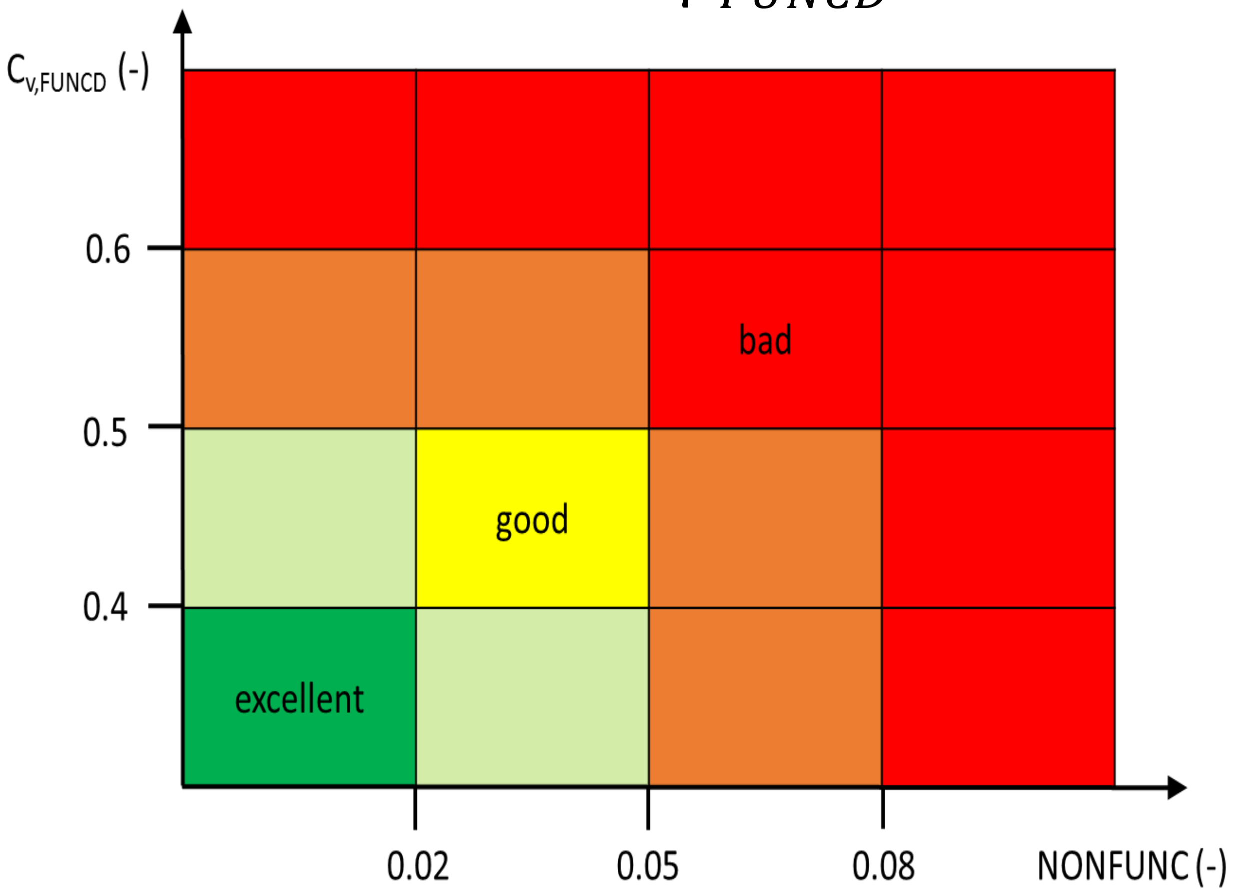
Van Steenberge *et al*. *Macromolecules* **2015**, 48, 7765
Van Steenberge *et al*. *Nat. Commun.* **2019**, to be subm.

CONCEPT OF FUNCTIONALITY-CHAIN LENGTH DISTRIBUTION

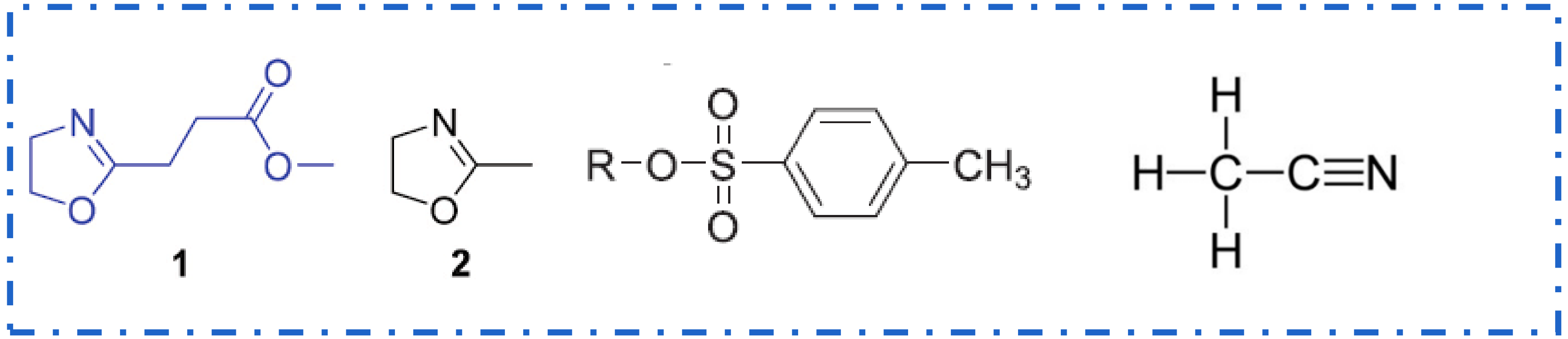


derived properties

$$C_{v,FUNCD} = \frac{\sigma_{FUNCD}}{\mu_{FUNCD}}$$



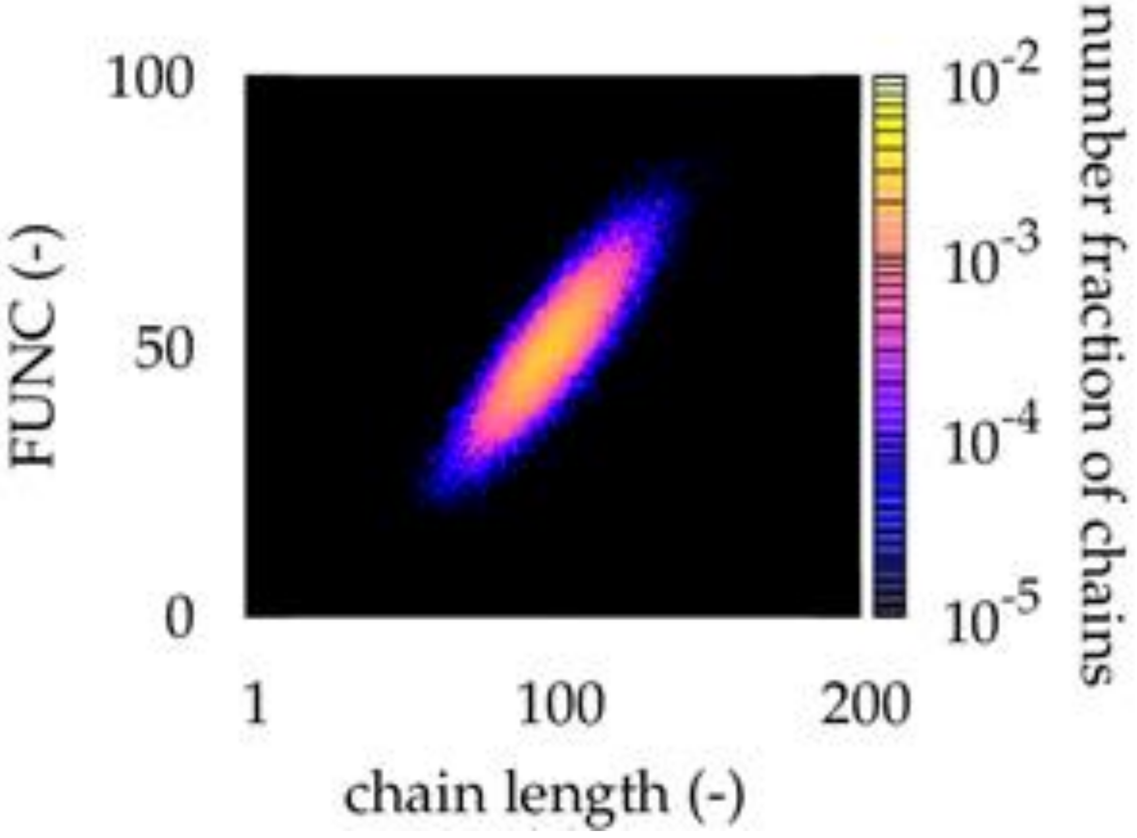
APPLICATION FOR CROP OF MEOX AND C2MESTOX: 1. EQUIMOLAR



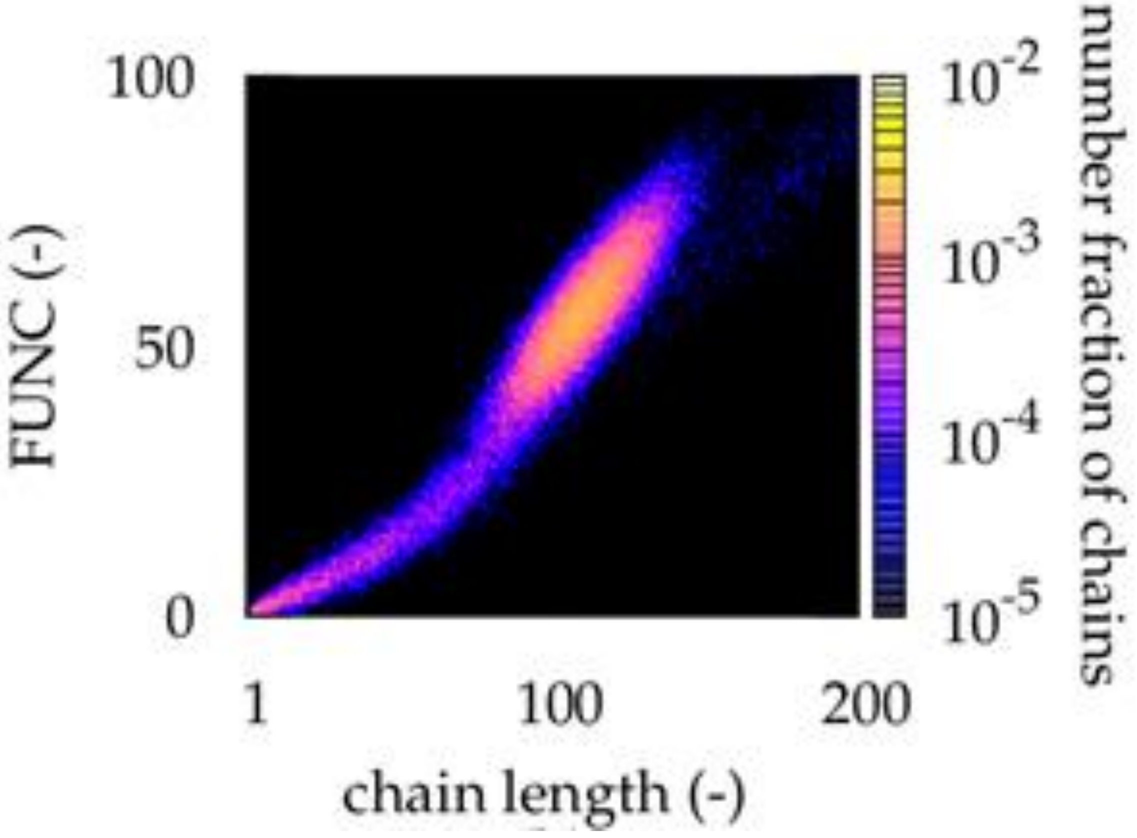
fingerprint of copolymer product quality

rate coefficients cf. first part

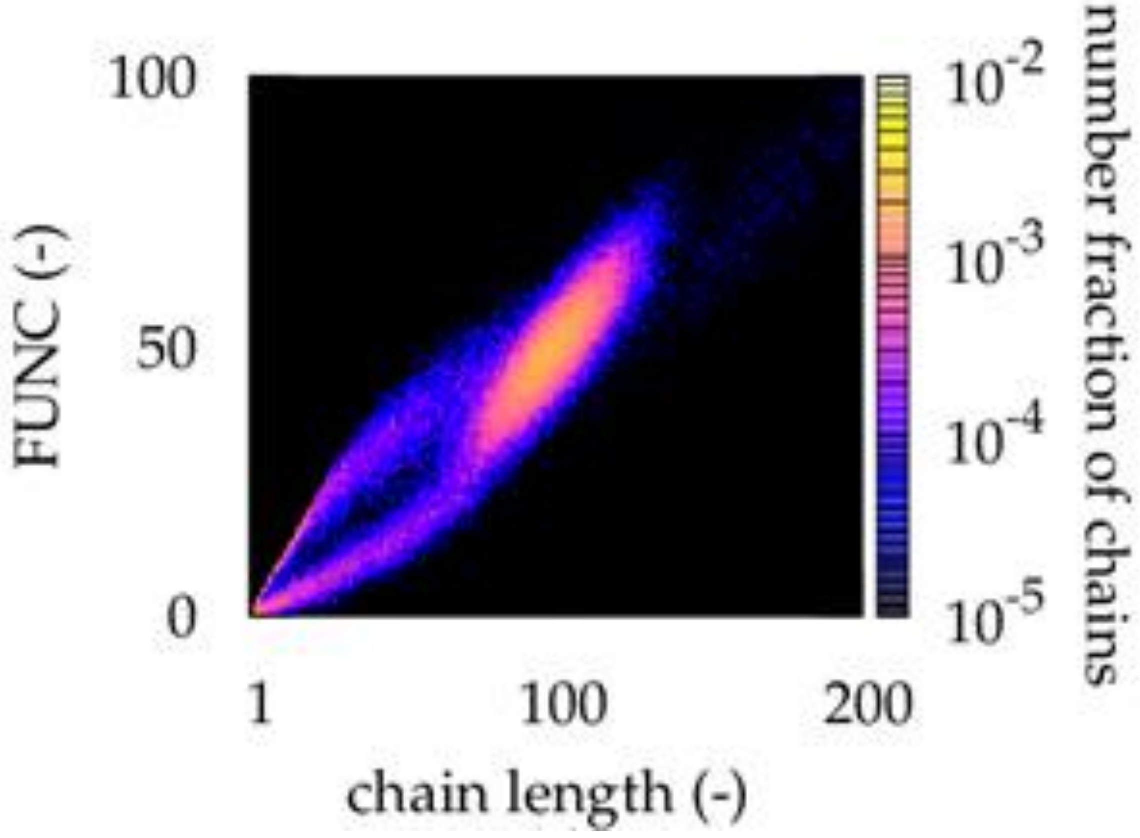
no side reactions



chain transfer to monomer

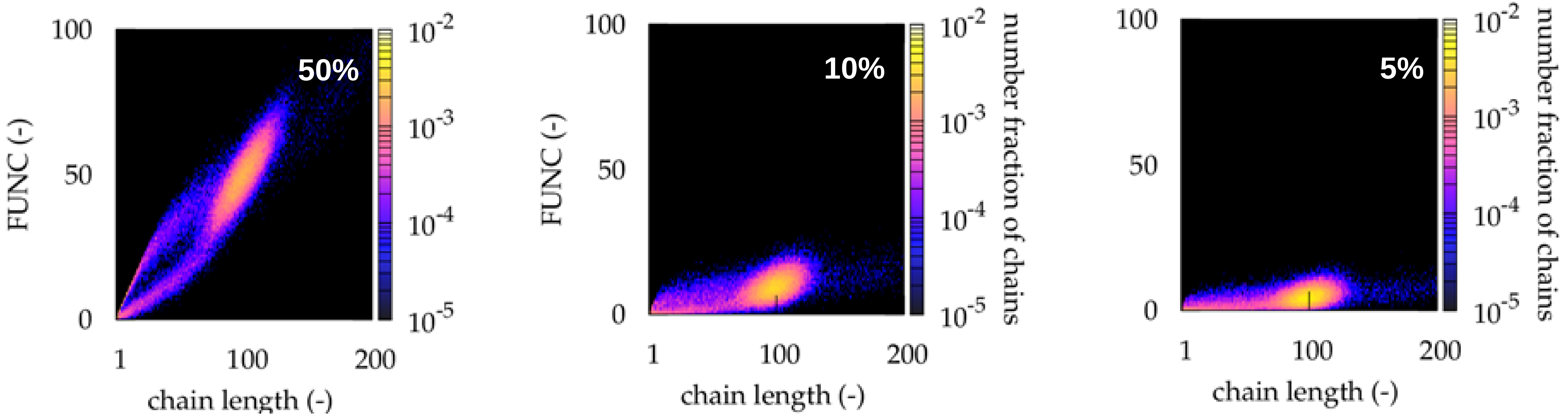


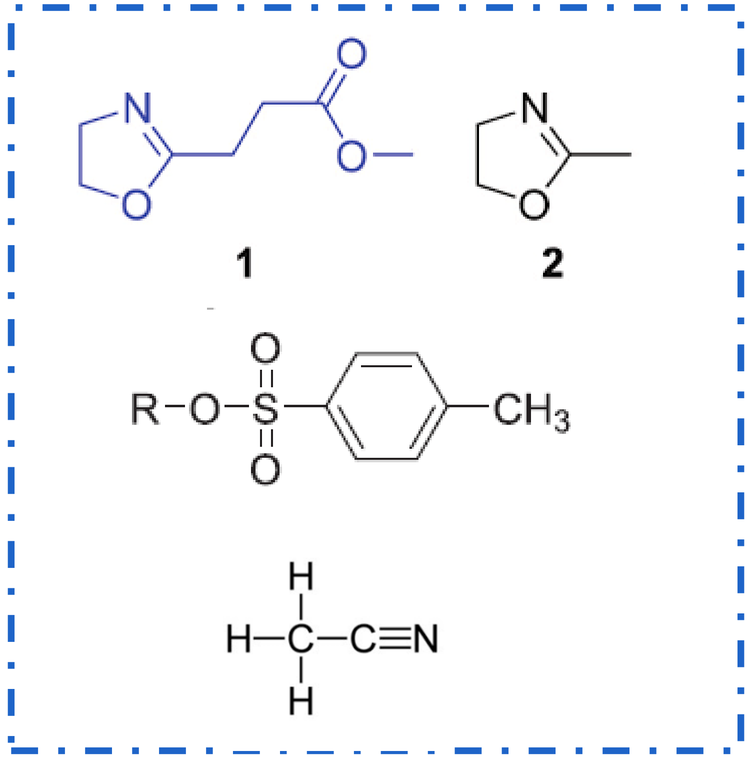
+ extra chain initiation & macropropagation

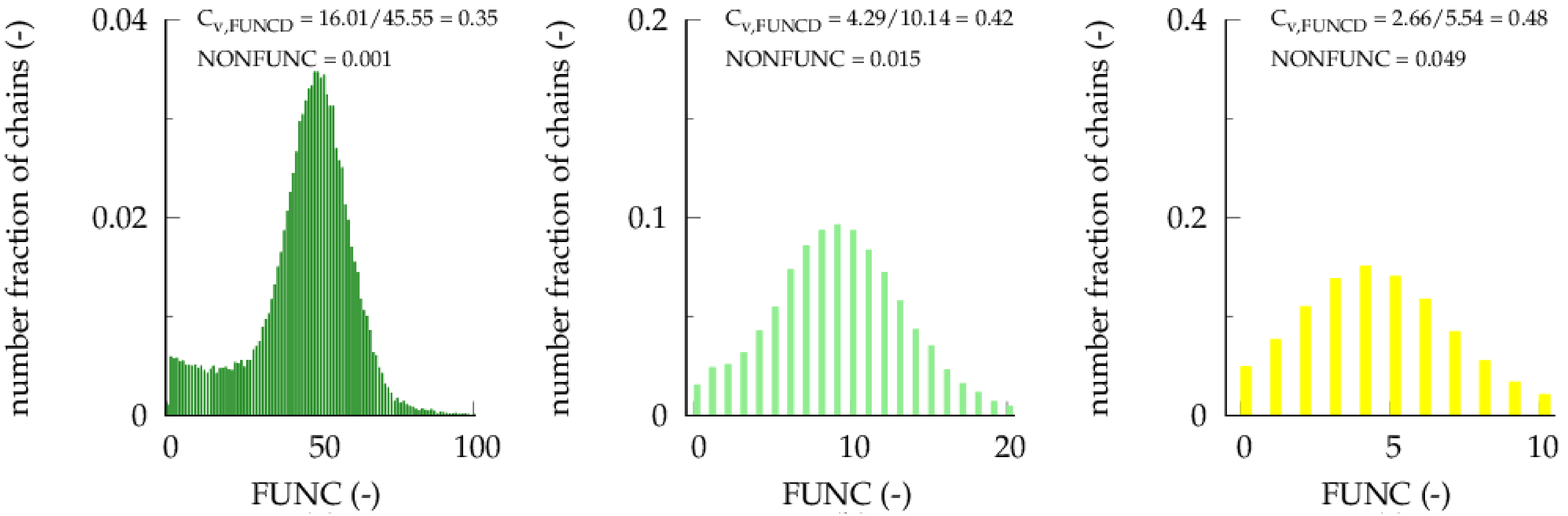


total monomer concentration: 3 mol L^{-1}; solvent acetonitrile; target DP of 100; 413 K; overall monomer conversion of 100%

APPLICATION FOR CROP OF MEOX AND C2MESTOX: 2. LOWER AMOUNTS



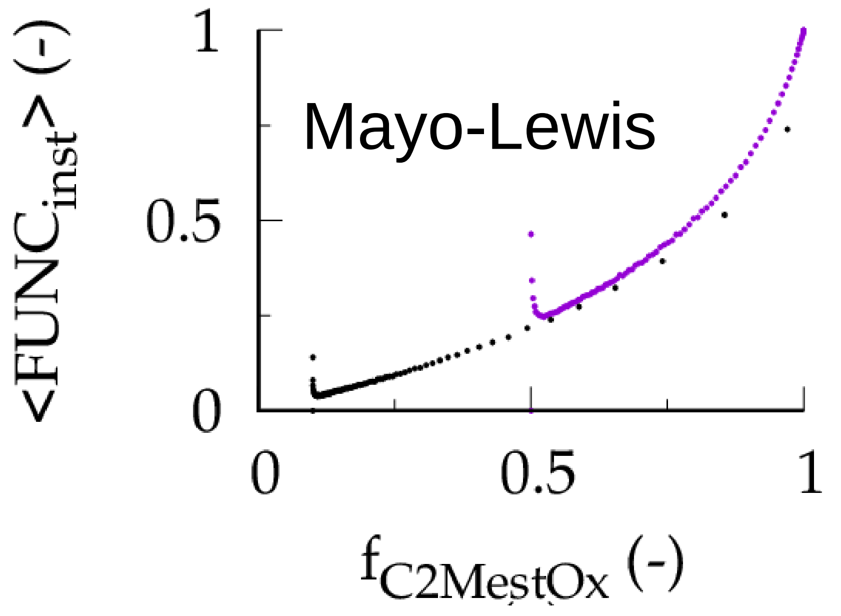


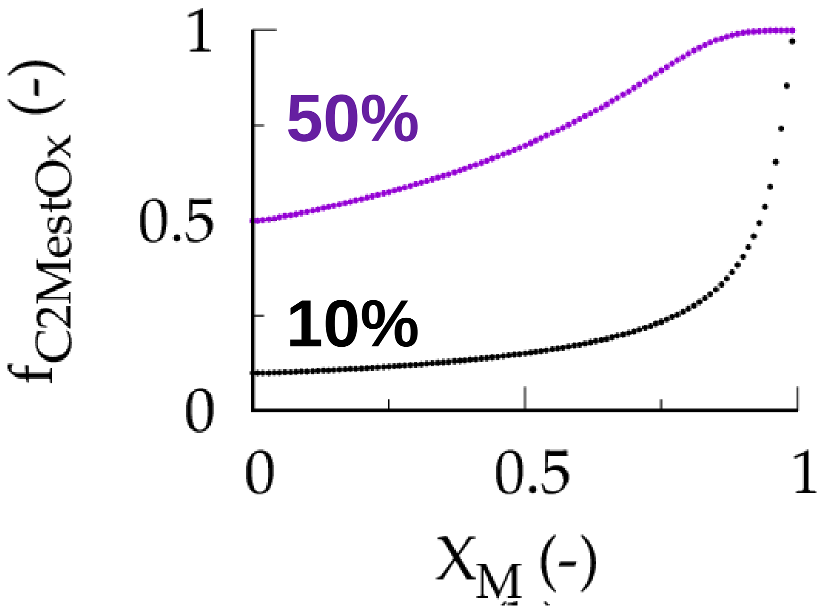


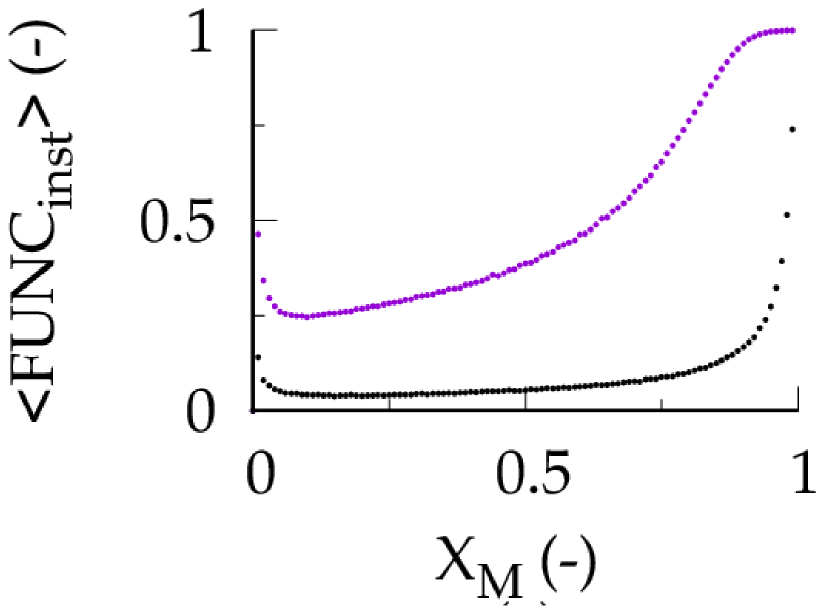
APPLICATION FOR CROP OF MEOX AND C2MESTOX

Unbiased in contrast to conventional average characterization

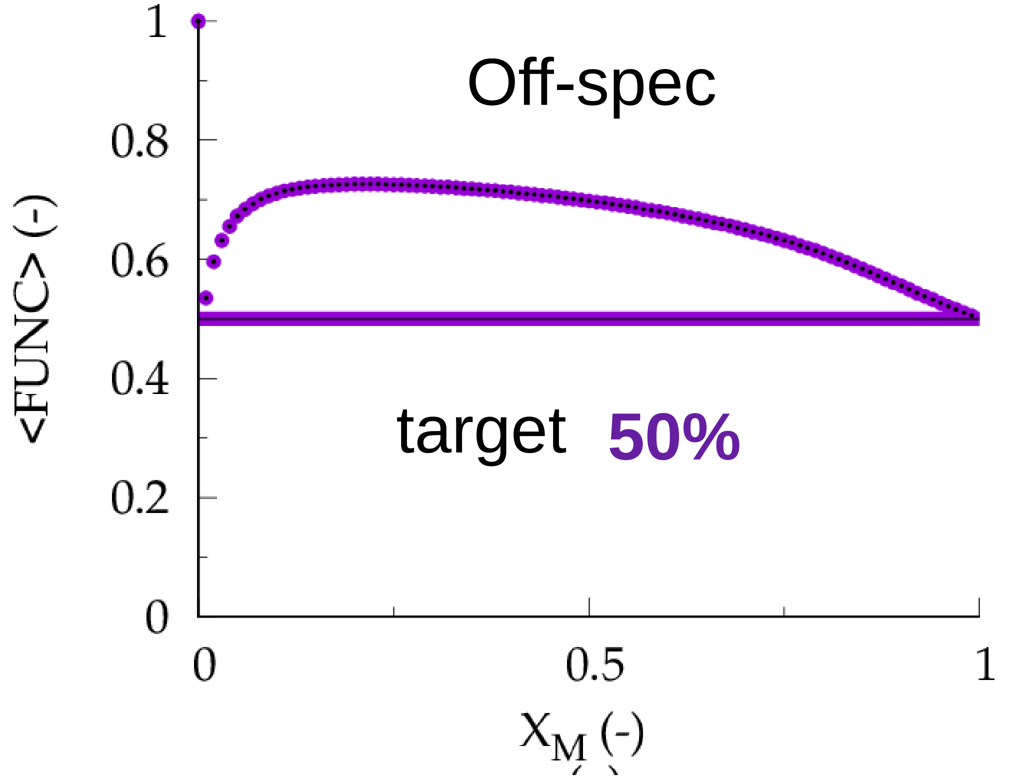
Instantaneous







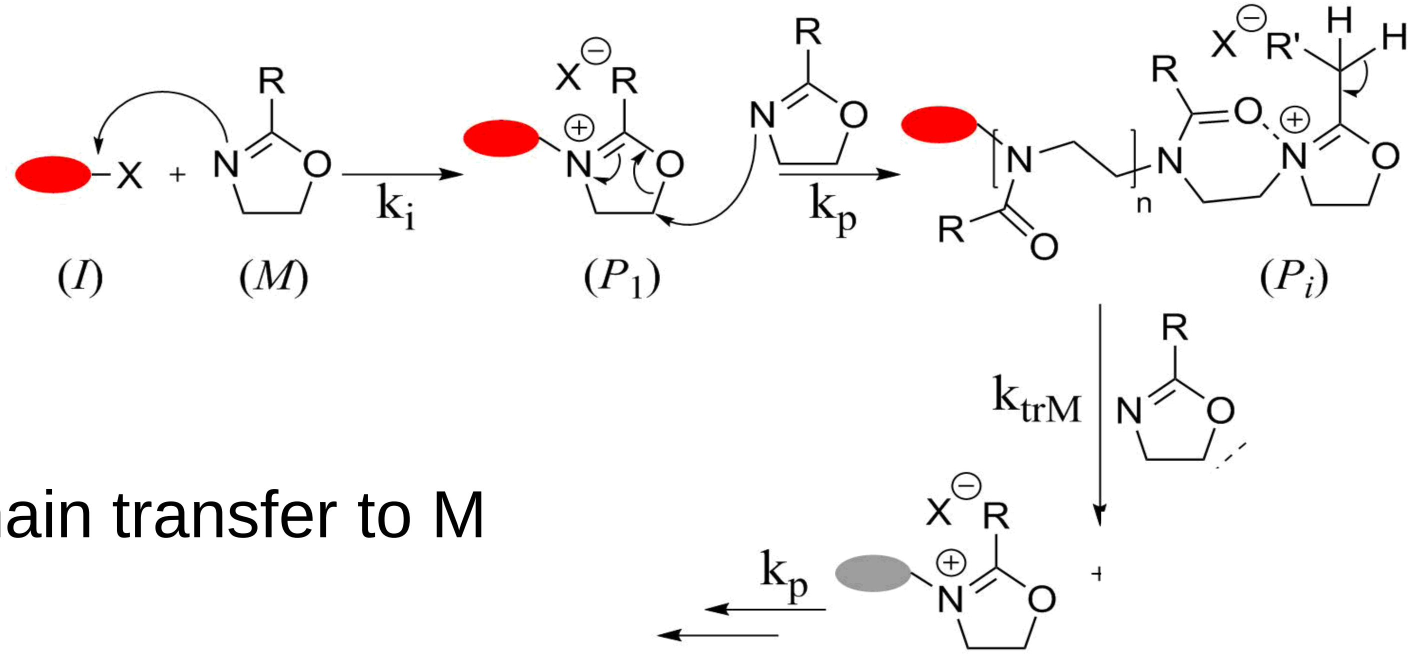
Cumulative



Chain length history not included

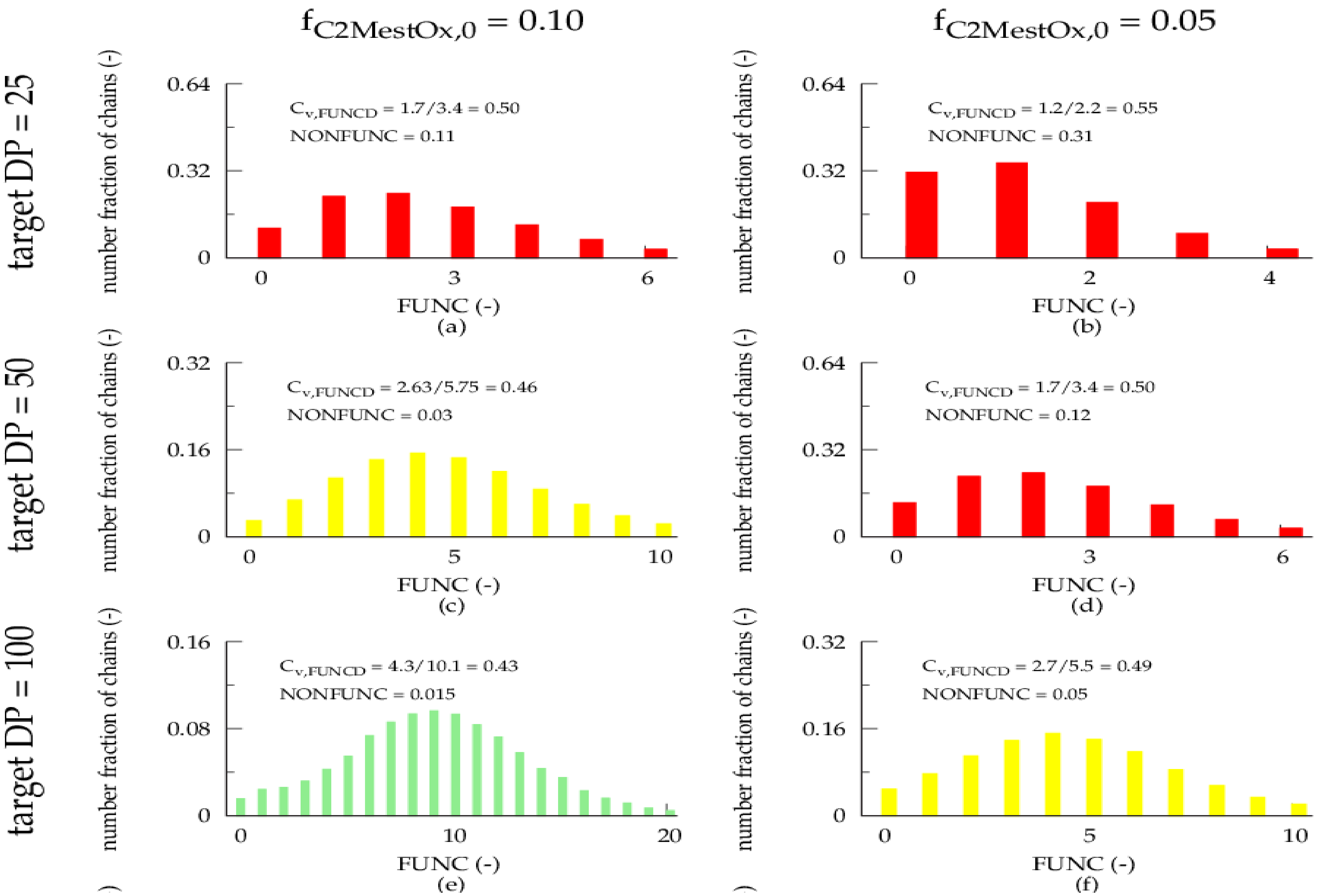
side reactions masked

Same results with and without chain transfer to M



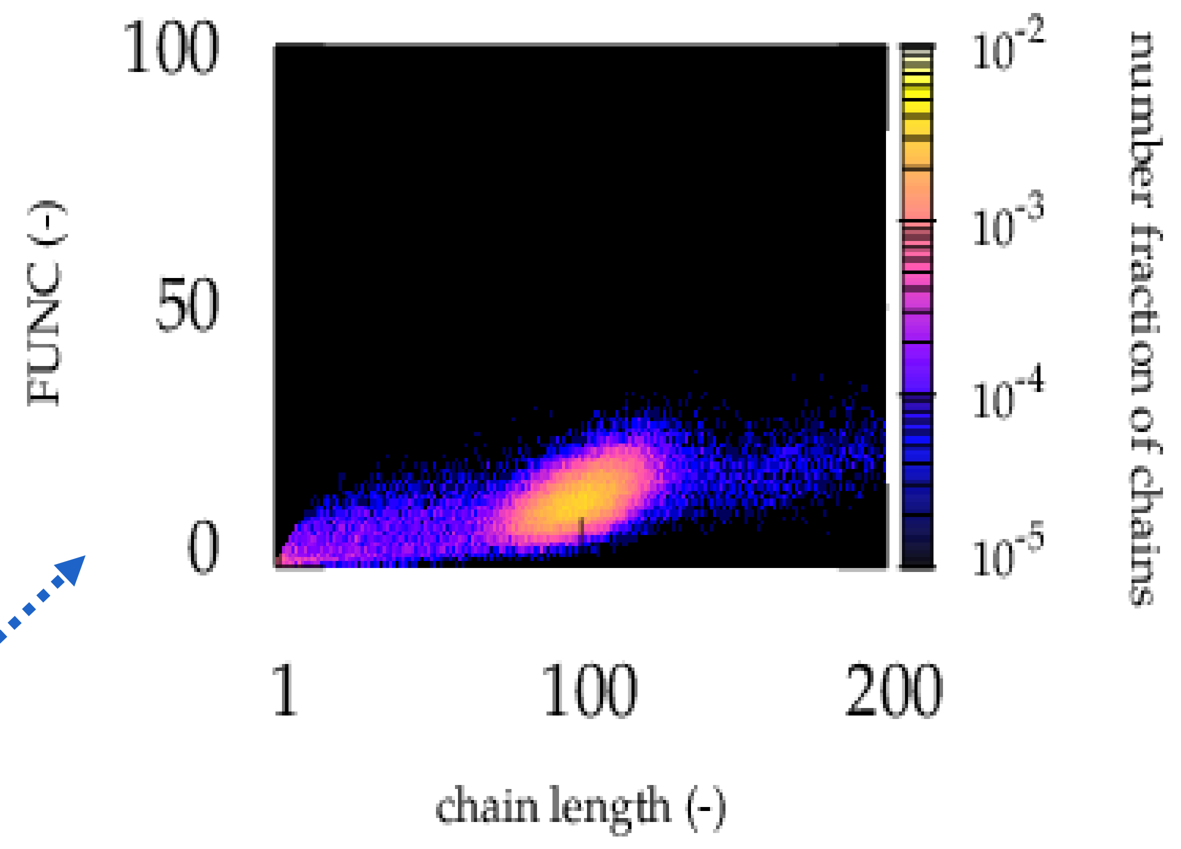
STRENGTH OF MODEL: FULL SCREENING OF CONDITIONS

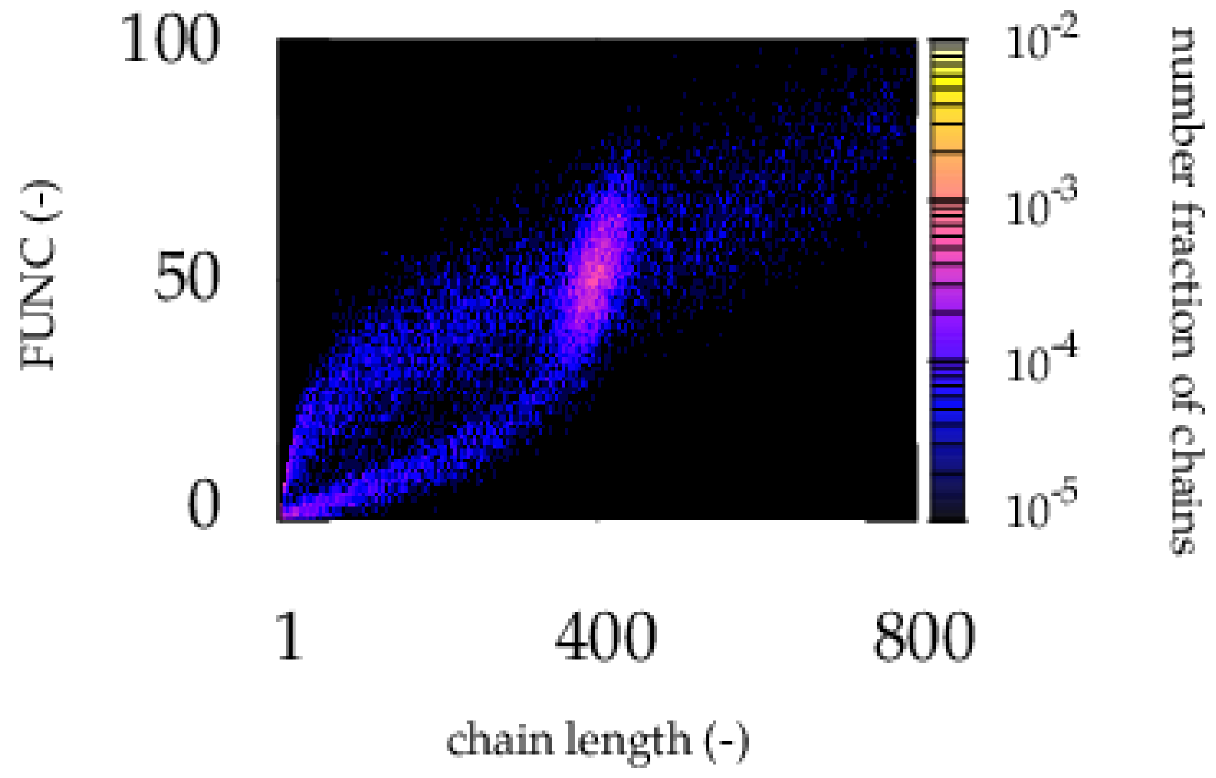
e.g. 6 cases



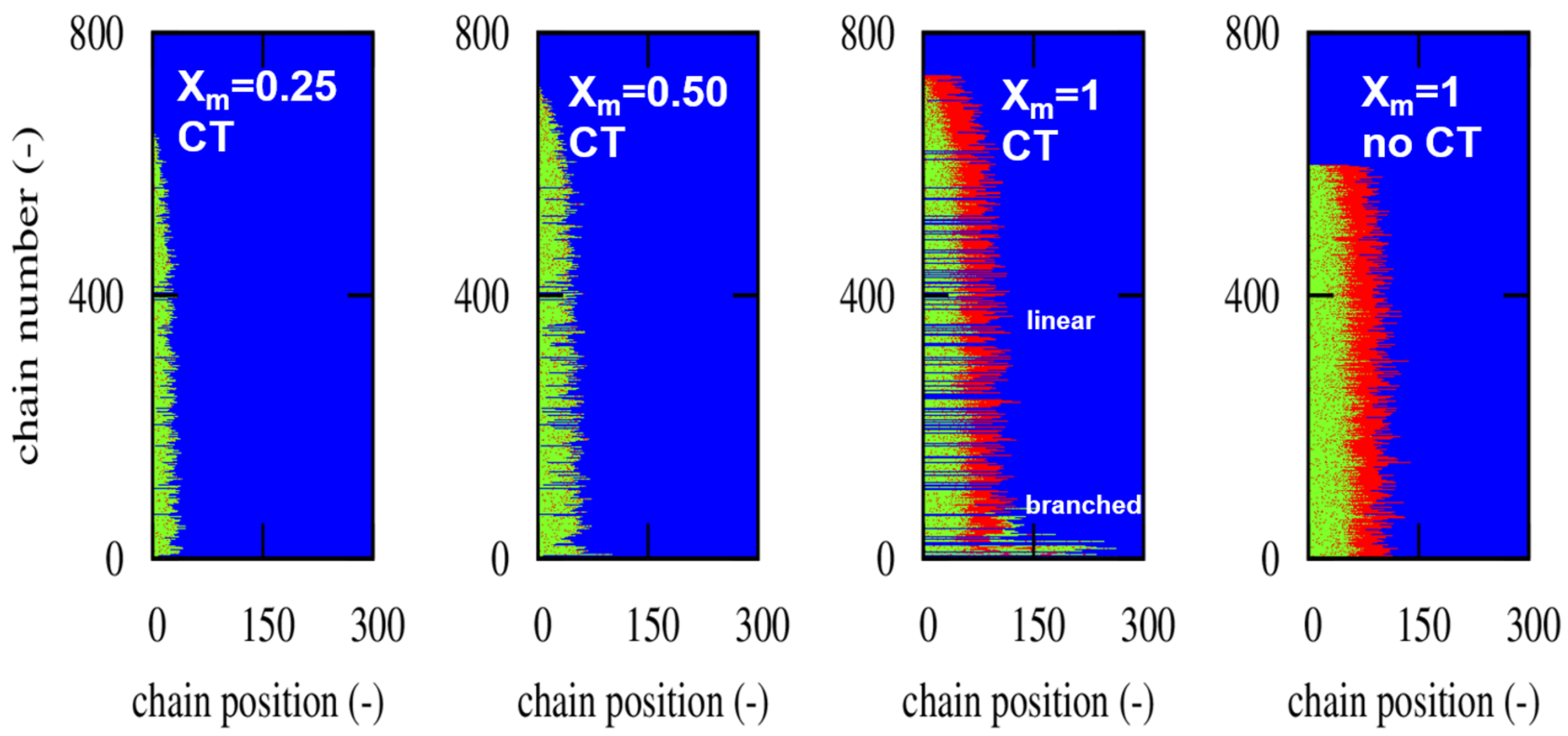
STRENGTH OF MODEL: DESIGN OF CROP PROCESS

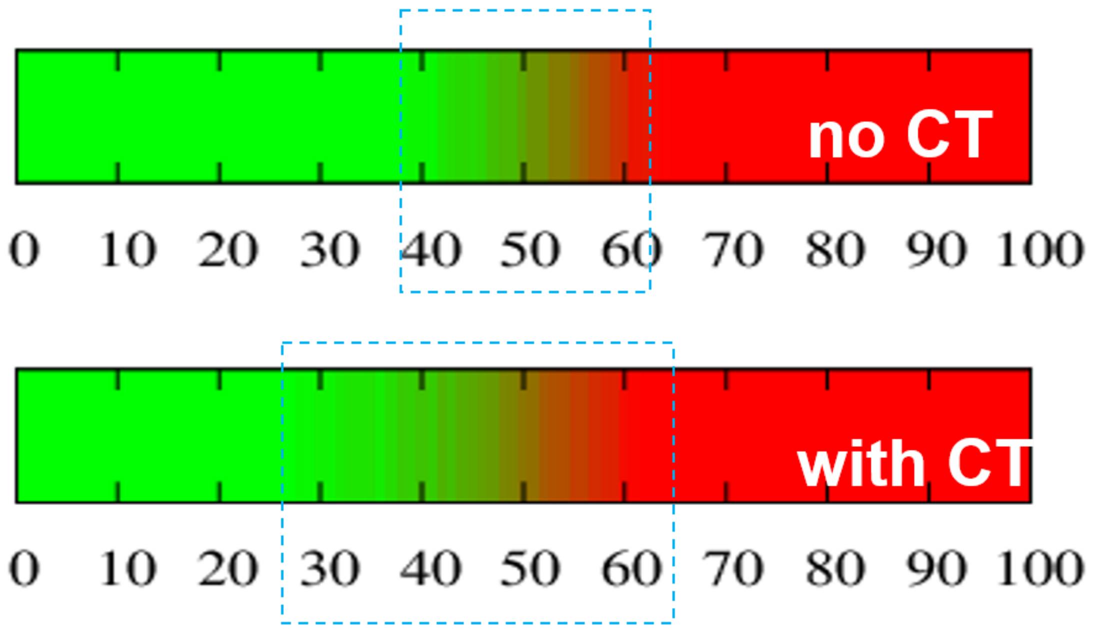
Reaction conditions		$C_{v,FUNCD}$ & NONFUNC (-)	
		MeOx/C2MestOx	EtOx/C2MestOx
1	$f_{C2Mest0x,0}$=0.02; target DP=100; T=100°C	0.527 & 0.195	0.522 & 0.213
2	$f_{C2Mest0x,0}$=0.02; target DP=100; T=140°C	0.531 & 0.205	0.539 & 0.238
3	$f_{C2Mest0x,0}$=0.02; target DP=400; T=100°C	0.554 & 0.072	0.627 & 0.106
4	$f_{C2Mest0x,0}$=0.02; target DP=400; T=140°C	0.602 & 0.101	0.677 & 0.137
5	$f_{C2Mest0x,0}$=0.10; target DP=100; T=100°C	0.415 & 0.012	0.413 & 0.019
6	$f_{C2Mest0x,0}$=0.10; target DP=100; T=140°C	0.424 & 0.015	0.447 & 0.026
7	$f_{C2Mest0x,0}$=0.10; target DP=400; T=100°C	0.497 & 0.011	0.599 & 0.014
8	$f_{C2Mest0x,0}$=0.10; target DP=400; T=140°C	0.564 & 0.018	0.672 & 0.021
9	**$f_{C2Mest0x,0}$=0.13; *target DP=100*; T=100°C**	**0.393 & 0.008**	0.396 & 0.011
10	$f_{C2Mest0x,0}$=0.13; target DP=100; T=140°C	0.411 & 0.012	0.432 & 0.016
11	**$f_{C2Mest0x,0}$=0.13; *target DP=400*; T=100°C**	**0.481 & 0.008**	0.593 & 0.009
12	$f_{C2Mest0x,0}$=0.13; target DP=400; T=140°C	0.561 & 0.013	0.664 & 0.013





NEXT STEP: MONOMER SEQUENCES: E.G. GRADIENT CASE





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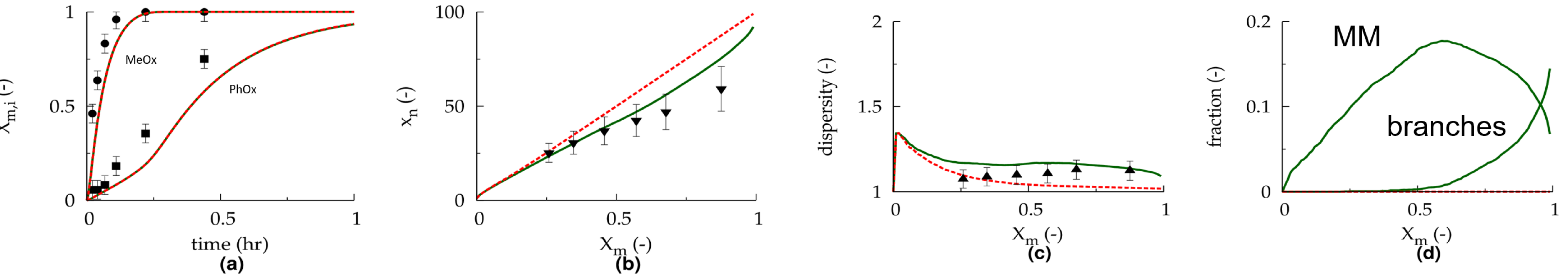
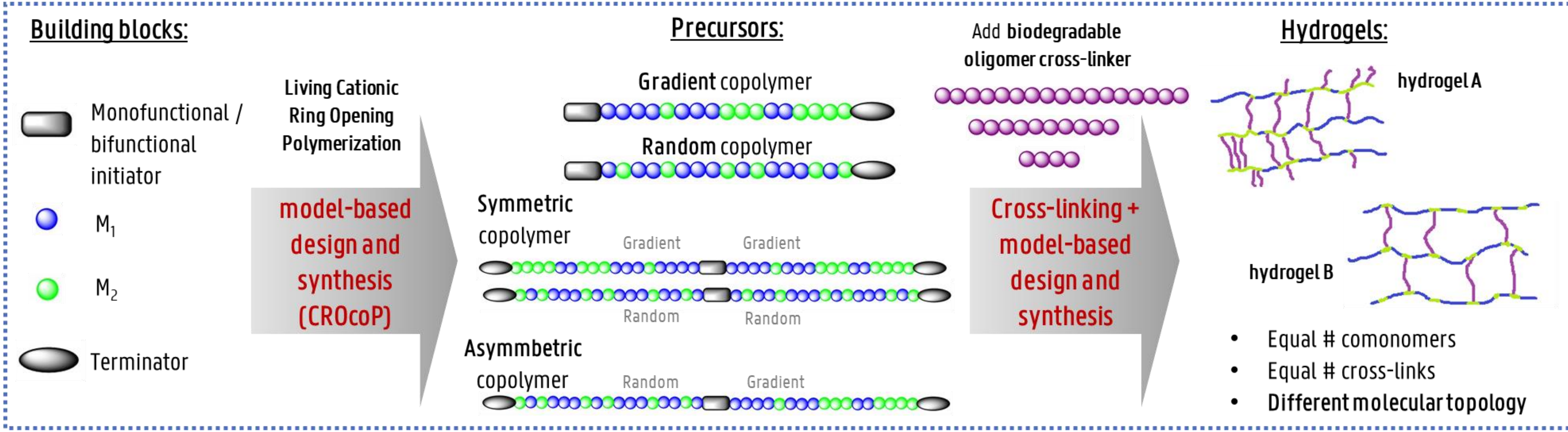


140°C; $[MeOx]_0$:$[PhOx]_0$: $[MeOTs]_0$ = 50:50:1; $[MeOx]_0$+$[PhOx]_0$ = 3 mol L^{-1}; solvent: acetonitrile

FUTURE OUTLOOK



CONCLUSIONS

1. Modeling & experimental work allow to understand CROP of 2-oxazolines
    - chain initiation reactivity: In and low conversion dispersity data
    - chain transfer to M reactivity: high monomer conversion dispersity data
    - macropropagation reactivity: SEC trace data
    - access to absolute MMD data for all macrospecies types
    - simple method to assess branching fraction

2. The strength is further clear upon the transition to copolymerization with functional M
    - FUNC-CLD and derived properties allow for an unbiased qualification
    - After parameter tuning all experimental possibilities can be screended
    - optimal synthesis conditions can be identified for low and high target DPs

ACKNOWLEDGEMENTS

1. Special research fund Ghent University

2. FWO Vlaanderen

3. China Scholarship Council

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